"PROGNOSTIC EFFICACY OF CEREBROSPINAL FLUID GAMMA GLUTAMYL TRANSPEPTIDASE IN PYOGENIC AND TUBERCULOUS MENINGITIS – A CROSS-SECTIONAL STUDY"

By

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Dissertation submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D. MEDICINE

Under the Guidance of

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DECLARATION

I hereby declare that this dissertation entitled **"PROGNOSTIC EFFICACY OF CEREBROSPINAL FLUID GAMMA GLUTAMYL TRANSPEPTIDASE IN PYOGENIC AND TUBERCULOUS MENINGITIS – A CROSS-SECTIONAL STUDY"** is a bonafide and genuine research work carried out by me under the guidance of **Dr. SRINIVAS B.** $_{\mathbf{MD}}$ Professor, Department of Medicine, Jawaharlal Nehru Medical College, Nehru Nagar, Belgaum – 590 010.

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LIST OF ABBREVIATIONS USED

ADA	–	Adenosine deaminase
AFB	–	Acid fast bacilli
ALP	_	Alkaline phosphatase
AST	_	Aspartate transaminase
CK	_	Creatine kinase
CKBB	_	Creatine kinase brain isomer
CN	–	Cranial Nerve
CNS	_	Central nervous system
CPK	_	Creatine phosphokinase
CRP	_	C- Reactive protein
CSF	_	Cerebrospinal fluid
CT	–	Computed Tomography
CVT	–	Cortical venous thrombosis
DNA	_	Deoxyribose nucleic acid
DOA	_	Date of admission
DOD	_	Date of discharge
DOE	_	Date of expiry
E. Coli	_	Escherichia coli
ELISA	_	Enzyme linked immunosorbent assay
ESR	–	Erythrocyte Sedimentation Rate
Exp	_	Expired
FNAC	_	Fine needle aspiration cytology
GCNA	_	γ-glutamyl – 3 carboxy – 4-nitranilide
GGT	–	Gamma Gutamyl Transpeptidase

H_2O	_	Hydrogen oxide
H. influenzae	_	Haemophilus Influenzae
HIV	_	Human immunodeficiency virus
ICP	_	Intracranial pressure
IFCC	_	International federation of clinical chemistry
IP	–	In patient
LA	_	Latex agglutination
LDH	_	Lactate dehydrogenase
MRI	_	Magnetic resonance imaging
n	_	Number
N. meningitidis	_	Nisseria meningitidis
PCR	_	Polymerase chain reaction
PM	–	Pyogenic Meningitis
RNA	_	Ribose nucleic acid
SA	–	Spinal Anaesthesia
S. pneumoniae	_	Streptococcus pneumoniae
Surv	_	Survivors
TB	–	Tuberculosis
TBM	–	Tuberculous Meningitis
ULN	_	Upper limit of normal
UTI	_	Urinary tract infection
VDRL	_	Venereal disease research laboratory.
WNV	_	West Nile Virus
Z-N	_	Ziehl – Neelson

ABSTRACT

Background and objectives

Gamma glutamyl transpeptidase was measured serially in cerebrospinal fluid in 40 cases of meningitis with the aim to find out its prognostic significance in cases of pyogenic and tuberculous meningitis.

Methods

The enzymatic activity was measured serially on day one and five in cerebrospinal fluid in 40 cases of meningitis consisting of 22 cases of pyogenic and 18 cases of tuberculous meningitis and 10 age and sex matched healthy control. The clinical details including the level of consciousness and neurological deficits were correlated with the enzymatic activity and prognosis.

Results

The levels of cerebrospinal fluid gamma glutamyl transpeptidase were significantly elevated in all the cases (75.05 ± 38.27 IU/L) of meningitis as compared to controls (5.60 ± 1.81 IU/L). The activity was significantly higher in pyogenic than in tuberculous meningitis. The maximum elevation in activity of gamma glutamyl transpeptidase was seen on the first day thereafter the activity declined in the majority of cases who had shown clinical improvement. However in 10 cases (seven pyogenic meningitis, three tuberculous meningitis), the enzymatic activity on day five, persistently remained high. All these 10 cases died. Further, the basal enzymatic activity in all these 10 cases that died (110.20 ± 24.14 IU/L) was higher compared to those who survived (63.33 ± 34.94 IU/L).

Conclusions and interpretation

It is concluded that cerebrospinal fluid gamma glutamyl transpeptidase was significantly elevated in cases of meningitis. It was not possible to differentiate the type of meningitis on the basis of enzymatic activity in any of them. However, it was possible to predict prognosis because higher basal activity and persistent high level were associated with poor prognosis.

Key words

Meningitis; Pyogenic; Tuberculous; Cerebrospinal fluid; Gamma Glutamyl Transpeptidase;

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INTRODUCTION

Acute Infections of the nervous system are among the most important problems in medicine because early recognition, efficient decision making and rapid institution of therapy can be life saving.

Among the chronic meningitis, tuberculous meningitis remains as important cause of morbidity and mortality in India.

Meningitis is still associated with high mortality rate and severe neurological sequelae. In general the risk of death from bacterial meningitis increases with decreased level of consciousness, seizures, raised intracranial pressure (ICP), extremes of age, comorbid conditions, delay in initiation of treatment, decreased cerebrospinal fluid (CSF) glucose and marked elevation of CSF protein.[1] But there is no single prognostic marker. Any test which facilitate in prognostication should be very valuable.

Gamma glutamyl transpeptidase (GGT) is an enzyme present in plasma membrane and helps in transfer of certain amino acids across it. It is present in renal tubular cells, bile ductule cells, endoplasmic reticulum of hepatocytes, seminal vesicles, pancreas, spleen, heart and neural cell membrane in the brain.[2] GGT levels are elevated in CSF of meningitis patients (pyogenic and tuberculous) and correlate with clinical picture, predict prognosis, because higher basal activity and serial rise were associated with poor prognosis.[2]

OBJECTIVES

The objectives of present study are;

1. To estimate the gamma glutamyl transpeptidase levels in cerebrospinal fluid serially on day one and day five of admission in patients with pyogenic and tuberculous meningitis
2. To evaluate whether gamma glutamyl transpeptidase levels have prognostic significance in cases of pyogenic meningitis and tuberculous meningitis.

REVIEW OF LITERATURE

HISTORICAL REVIEW

The history of meningitis dates back to 300 BC when its existence was shown by Edwin Smith Papyrus.

1806	:	Danielson and Mann have given the first account of cerebrospinal meningitis in American literature.[3]
1810	:	Reverend Foster gave a graphic description of an outbreak of meningococcemia and meningococcal meningitis.[3]
1863	:	Cryptococcosis was recognized.[4]
1882	:	The tubercle bacilli were discovered by Robert Koch.[5]
1887	:	Weischselbaum described Nisseria meningitidis (N. meningitidis) as the causative agent of meningitis.[6]
1887	:	Bruce grew brucella and named it Micrococcus melitensis.[3]
1890	:	Bakten showed that meninges could be involved as a result of hematogenous spread.[3]
1891	:	Quincke devised the diagnostic lumbar puncture.[3]
1893	:	Licktheim isolated tubercle bacilli from CSF.[3]
1893	:	Walter showed that the blood CSF barrier to bromide is altered in tuberculous meningitis.[3]
1894	:	Cryptococcosis was described in more detail by Busse.[4]

1895 : The fungus was isolated from material of a patient by Busse.[4]

1897 : Bang isolated Brucella abortus.[3]

1913 : Simon Flexner first reported some success in treating bacterial meningitis with intrathecal equine meningococcal antiserum.[7]

1924 : Brucella was first isolated from a patient by Keefer in Baltimore.[3]

1932 : Burr and Finley studied the role of immunity in tuberculous meningitis by injecting tubercle protein in the cisterns of controls and hypersensitive animals.[3]

1933 : Rich and Maccrodale challenged the hematogenous spread after doing autopsy studies and put forth the Rich focus theory.[3]

1933 : Lancefield introduced her technique for the precipitin grouping of Streptococci.[6]

1958 : Udani and Dastur showed that tuberculous meningitis could present in the form of encephalopathy. [3]

1969 : Dastur and Wadia showed that tuberculous meningitis could present as spinal arachnoiditis. [3]

1980 : Antonine Jesse noticed that tuberculous meningitis was more often associated with tuberculosis (TB) of other organs.[3]

ANATOMY OF MENINGES

The brain is covered by three membranous coverings (meninges): The outer dura meter, the middle arachnoid mater and the inner pia mater. The cerebrospinal fluid fills the space between the arachnoid and the pia (Subarachnoid space).

The dura mater is made up of two layers, an outer endosteal layer and an inner meningeal layer, enclosing the cranial venous sinuses between the two. The meningeal layer forms four folds which divide the cranial cavity into intercommunicating compartments.

The arachnoid mater is a thin transparent membrane that loosely surrounds the brain without dipping into its sulci. It bridges all irregularities of the brain, with the exception of the longitudinal fissure and the stem of the lateral sulcus.

The pia meter is a thin vascular membrane which closely invests the brain, dipping into various sulci and other irregularities of its surface. It is better defined around the brainstem.

Subarachnoid space is the space between the arachnoid and the pia mater. It is traversed by a network of arachnoid trabeculae which give it a sponge-like appearance. It surrounds the brain and spinal cord, and ends below at the lower border of the second sacral vertebra. It contains CSF and large vessels of the brain. Cranial nerves pass through this space.

CEREBROSPINAL FLUID

Formation and Absorption

CSF fills the ventricles and subarachnoid space. It is mainly formed in the choroid plexuses of the cerebral ventricles. The CSF in the ventricles flows through the foramina of Magendie and Luschka to the subarachnoid space and is absorbed through the arachnoid villi into the cerebral venous sinuses.

Lumbar CSF pressure is normally 70 to 180 mm CSF. The pH of CSF is 7.33. Normal protein content is 15 to 40 mg/dL and the normal glucose is 40 to 80 mg/dL. Normal CSF contains less than five cells/mm^3 mainly lymphocytes.

Functions of CSF

- Supports the brain and cerebral venous sinuses.
- Protects the brain from shock.
- It has a nutritive function.
- It also serves as a pathway for excretion from the central nervous system (CNS).

CSF can be obtained by;

a) Lumbar puncture
b) Cisternal puncture
c) Ventricular puncture

Lumbar puncture is the easiest method and is commonly used.

LUMBAR PUNCTURE

Procedure

The patient lies with his/her back on the edge of the bed in the left lateral position with his/her knees drawn up. In adults, the L3 to L4 intervertebral space is marked. The part is cleaned with iodine and spirit and anaesthetized with 2%

lignocaine. Then the spinal needle is inserted aiming towards the umbilicus. We feel resistance while passing through the spinal ligaments and dura mater. After passing through these structures, we notice reduced resistance as the needle enters the subarachnoid space. After withdrawing the stylet, CSF can be collected. After collecting the CSF, the needle is withdrawn and the puncture site is sealed with a tincture benzoin seal.[8,9]

Indications

Diagnostic

Absolute

Meningitis and subarachnoid haemorrhage.

Relative

Multiple sclerosis, Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy, unexplained coma, measurement of CSF pressure.

Therapeutic

- Intrathecal administration of drugs to treat pain and severe spasticity and malignancies.
- Removal of CSF in benign intracranial hypertension.

Contraindications

- Raised intracranial pressure

- Intracranial lesion with mass effect
- Clotting abnormalities
- Local infection

Complications

i) Post lumbar puncture headache – about one third of patients develop a post lumbar puncture headache within 24 hours.

ii) Coning can occur if a lumbar puncture is done in cases of raised intracranial pressure.

iii) Infections if proper aseptic precautions are not taken.

AETIOLOGY OF MENINGITIS

1. **Bacterial Causes**

   - Streptococcus pneumoniae
   - Nisseria meningitidis
   - Group B Streptococci
   - Listeria monocytogenes
   - Haemophilus influenzae
   - Enteric gram-negative bacilli
   - Staphylococcus aureus and Coagulase-negative Staphylococci
   - Treponema pallidum
   - Borrelia burgdorferi
   - Actinomyces, nocardia, brucella, tropherema whippelii

- Leptospira

2. Mycobacterial causes

- Mycobacterium tuberculosis and others.

3. Viral Causes

- Enteroviruses like Coxsackie viruses, echoviruses, polioviruses and human enteroviruses 68 and 71.
- Arboviruses
- Herpes simplex virus 1 and 2
- Lymphocytic choriomeningitis virus
- Varicella-Zoster virus
- Mumps
- Human immunodeficiency virus (HIV)
- Epstein-Barr virus
- Cytomegalovirus

4. Fungal Causes

- Cryptococcus neoformans
- Histoplasma capsulatum
- Coccidioides immitis
- Candida albicans
- Blastomyces dermatitidis
- Aspergillus species
- Sporothrix schenckii

- Xylohypha
- Trichoides
- Curvularia
- Drechslera, mucor, pseudoallescheria boydii

5. Protozonal Causes

- Toxoplasma gondii
- Trypanosomiasis
    - Trypanosoma gambiense
    - Trypanosoma rhodesiense
- Acanthamoeba

6. Helminithic Causes

- Cysticercosis
- Gnathostoma spinigerum
- Angiostrongylus cantonensis
- Baylisascaris procyonis
- Trichinella spiralis
- Echinococcus cysts
- Schistosoma species

7. Non-infectious Causes

- Malignancy
- Chemical compounds
- Primary inflammation like

  - CNS sarcoidosis
  - Vogt-Koyanagi-Harada syndrome
  - Isolated granulomatous angitis of the nervous system
  - Systemic lupus erythematosus
  - Behcet's syndrome
  - Chronic benign lymphocytic meningitis
  - Drug hypersensitivity
  - Wegener's granulomatosis

- Others: Multiple sclerosis, Sjogren's syndrome, neonatal onset multisystemic inflammatory disease and rarer forms of vasculitis (for example Cogan's syndrome)

Clinical Features[10]

- The classic clinical triad of meningitis is fever, headache and nuchal rigidity (stiff neck)
- Alteration in mental status
- Nausea, vomiting and photophobia
- Seizures
- Deteriorating or reduced level of consciousness, papilledema, dilated poorly reactive pupils, sixth nerve palsy, decerebrate posturing, bradycardia, hypertension and irregular respirations, signs of raised intracranial pressure.
- Focal neurological deficits like hemiplegia, cranial nerve palsies.

- Other non-specific features like malaise, myalgia, anorexia, abdominal pain and /or diarrhea, lethargy.
- Specific clinical features depending upon the etiology like – a petechial or purpuric rash or large ecchymoses in meningococcal meningitis.

Signs of Meningeal Irritation

- Neck retraction
- Arching of the back (opisthotonos)
- Curling of the body away from the light

Neck rigidity/Neck stiffness

This is tested by placing both hands under the occipital region and by flexing the wrists, the head is gently raised forwards until the chin rests on the chest. In meningeal irritation, this causes pain in the posterior part of the neck sometimes radiating down the back and the movement is resisted by spasm in the extensor muscles of the neck.

Kernig's Sign

This is tested with the patient supine on the bed by passively extending the patient's knee when the hip is flexed. In patients with meningeal irritation, this causes pain and spasm of the hamstrings.

Brudzinski's Sign

In Brudzinski's neck sign, there is flexion of the hips and knees on flexing the neck or turning it to one side.

In Brudzinski's leg sign, on flexing one lower extremity, the opposite limb flexes automatically.

Pathological and Clinical correlations in acute, subacute and chronic meningeal reactions

I. In acute meningeal inflammation

a. Pure pia-arachnoiditis: headache, stiff neck, Kernig's and Brudzinski's signs.

b. Subpial encephalopathy: Confusion, stupor, coma and convulsions.

c. Inflammatory or vascular involvement of cranial nerve roots: ocular palsies, facial weakness and deafness.

d. Thrombosis of meningeal veins: Focal seizures, focal cerebral defects such as hemiparesis, aphasia, etc.

e. Cerebellar or cerebral hemisphere herniation: due to swelling, causing upper cervical cord compression with quadriplegia or signs of midbrain-third nerve compression.

II. In more subactue and chronic forms of meningitis

A. Tension hydrocephalus: variable degrees of impairment of consciousness, decorticate postures, grasp and juck reflexes, and sphincteric incontinence.

B. Subdural effusion: impaired alertness, refusal to eat, vomiting, immobility and persistence of fever despite clearing of CSF.

C. Extensive venous or arterial infarction: unilateral or bilateral hemiplegia, decorticate or decerebrate rigidity, cortical blindness, stupor or coma with or without seizures.

III. Late effects or sequelae

A. Meningeal fibrosis around optic nerves or around spinal cord and roots: blindness and optic atrophy, and spastic paraparesis with sensory loss in the lower segments of the body.

B. Chronic meningoencephalitis with hydrocephalus: dementia, stupor or coma and paralysis.

C. Persistent hydrocephalus in the child: blindness, arrest of all mental activity, bilateral spastic hemiplegia.

DIAGNOSIS

Laboratory Diagnosis

Cerebrospinal Fluid Examination[10,11,12]

- CSF pressure is elevated

Cerebrospinal Fluid Cytology:

- Pleocytosis is diagnostic

- The number of leukocytes ranges from 250 to 1,00,000 per cubic millimeter in acute pyogneic meningitis. Neutrophils predominate (85-95% of the total).

- Lymphocytic pleocytosis (25-500 cells/mm^3) is seen in viral meningitis.

- Lymphocytic pleocytosis (10-500 cells/mm^3) is seen in tuberculous meningitis.

- Mononuclear or lymphocytic pleocytosis is seen in fungal meningitis. Eosinophils may be seen in the CSF in Coccidioides immitis meningitis.

- Mononuclear cell pleocytosis is seen in brucella meningitis.

Cerebrospinal Fluid Biochemistry

The CSF protein content is higher than 45 mg/dL in acute pyogenic meningitis, slightly elevated (20 to 80 mg/dL) in viral meningitis, in the range of 10 to 500 mg/dL in tuberculous meningitis, increased in fungal meningitis, brucella meningitis, etc.

The CSF glucose content is diminished usually to a concentration below 40 mg/dL or less than 40 percent of the blood glucose concentration in acute pyogenic meningitis, fungal, brucella or tuberculous meningitis, sarcoidosis of the CNS and meningeal carcinomatosis.

The glucose content is normal in viral meningitis.

Cerebrospinal Fluid Microscopy

- Gram's stain of the spinal fluid sediment permits identification of the causative agent in many cases of bacterial meningitis.
- Spinal fluid may show acid-fast bacilli in tuberculous meningitis (in 10 to 40% of cases).
- India ink smear may be positive in fungal meningitis.

Cerebrospinal Fluid Culture

Cultures of the spinal fluid may be positive in 70 to 90% of bacterial meningitis, and in ~50% of cases of tuberculous meningitis.

Cerebrospinal Fluid Adenosine Deaminase (ADA)

CSF ADA levels easily differentiate tuberculous meningitis from pyogenic, viral and toxoplasma meningitis when a cut off value of 10 U/L is taken. The sensitivity and specificity are 90% and 95% respectively.[13-30]

Serological Studies

- For some viruses, including many arboviruses such as West Nile Virus (WNV), serologic studies remain a crucial diagnostic tool.
- Latex agglutination (LA) test: The latex agglutination test may be positive in patients with meningitis due to S. pneumoniae, N. meningitidis, H. influenzae type b, E. coli and group B streptococci.

- The Limbus amebocyte lysate assay may be positive in case of Gram-negative meningitis.
- The cryptococcal polysaccharide antigen test is a highly sensitive and specific test for cryptococcal meningitis.
- CSF Venereal disease research laboratory (VDRL) is usually positive in syphilitic meningitis.
- P24 antigen in serum and CSF may be detected in case of HIV meningitis.
- Enzyme linked immuno sorbent assay (ELISA) may detect mycobacterial antigen and antibody in CSF of patients with tuberculous meningitis.[31-34]
- C-reactive protein (CRP) determinations by latex slide agllutination of CSF is very sensitive albeit not as specific method for differentiation of bacterial meningitis from other diseases affecting the CNS.
- CSF polymerase chain reaction (PCR) may be positive for viral-specific deoxyribose nucleic acid (DNA) or ribose nucleic acid (RNA) especially in cases of meningitis caused by enteroviruses, herpes simplex virus, Epstein – Barr virus, Varicella-zoster virus and Cytomaegalovirus.[35,36]
- PCR may be positive for mycobacterium tuberculosis DNA in tuberculous meningitis.[37]

Radio imaging

Magnetic resonance imaging (MRI)

Diffuse meningeal enhancement is often seen after the administration of gadolinium. MRI may also show abscesses, tuberculomas, venous occlusions and adjacent infarctions.[38]

Computed tomography (CT)

Meningeal enhancement may be seen after contrast administration. CT may also show abscesses, tuberculomas, venous occlusions and adjacent infarctions. CT is particularly useful in detecting lesions that erode the skull such as a sinus wall defect.[39]

Other Tests

- Detection of tuberculostearic acid in cerebrospinal fluid gives a sensitive and rapid diagnosis of tuberculous meningitis.[40]
- Bromide partition test: The partition of bromide ion between serum and CSF after a loading dose reflects the integrity of the blood-brain barrier. Serum/CSF bromide ratio (in simultaneous samples) less than 1.6 is found to be characteristic of tuberculous meningitis.[41]
- Estimation of free sialic acid and lactic acid in CSF: The contents of the acids are significantly higher in cases of pyogenic meningitis.[42,43]
- Estimation of Adenosine deaminase in CSF: The levels of this enzyme are significantly raised in CSF of patients with tuberculous meningitis.[44-45]

Gamma Glutamyl Transpeptidase

Gamma glutamyl transpeptidase (GGT) is an enzyme involved in the transfer of the gamma glutamyl residue from gamma glutamyl peptides to amino acids, H_2O and other small peptides.[46]

In most biologic systems, glutathione serves as the gamma glutamyl donor.[47]

$$\text{Glutathione} + \text{aminoacid} \xrightarrow{\text{GGT}} \text{Glutamyl – peptide} + \text{L-Cysteinyl glycine.}$$

There are no isoenzymes of GGT.

Expression of GGT in organism

The enzyme is present in normal human serum. In humans the highest GGT activity is found in liver and kidneys. Even though renal tissue has the highest concentration of GGT, the enzyme present in serum appears to originate primarily from hepatobiliary system. It is also found in pancreas, spleen, heart, brain and seminal vesicles.[46,48, 49,50]

The enzyme is present in cytoplasm (microsomes), but the larger fraction is located in the cell membrane.[51]

Physiological roles of GGT

The specific physiological function of GGT has not been clearly established, but it has been suggested that GGT is involved in peptide and protein synthesis, regulation of tissue glutathione levels, and the transport of amino acids across cell membranes.[46,51]

Clinical Application of Serum GGT [46,48,51]

Hepatobiliary Disease

In the liver, GGT is located in the canaliculi of the hepatic cells and particularly in the epithelial cells lining the biliary ductules. Because of these locations, GGT is elevated in virtually all hepatobiliary disorders, making it one of the most sensitive of enzyme assays in these conditions. Higher elevations are generally observed in biliary tract obstruction.

Drugs and GGT

Within the hepatic parenchyma, GGT exists to a large extent in the smooth endoplasmic reticulum and is, therefore subject to hepatic microsomal induction. Thus GGT levels will be increased in patients receiving enzyme inducing drugs such as warfrain, phenobarbital and phenytoin. Enzyme elevations may reach levels four times upper limit of normal (ULN).

Alcohol and GGT

Because of the effects of alcohol on GGT activity GGT assays are considered sensitive indicators of alcoholism, particularly occult alcoholism, when other indicators are lacking.[52]

Generally, enzyme elevation in alcoholics and heavy drinkers range form two to three times ULN, although higher levels have been observed.

- Unlike alkaline phosphatase (ALP), GGT is not increased in condition in which osteoblastic activity is increased. It is useful in differentiating the source of an elevated ALP level.

- GGT assays are also useful in monitoring the effects of abstention from alcohol.

Other liver disorders

- High elevators of GGT are also observed in patients with either primary or secondary liver neoplasm.

- Moderate elevations (two to five times normal) occur in infectious hepatitis.

- Small increase of GGT activity are observed in patients with fatty liver and similar but transient increases are noted in cases of drug intoxication.

In pancreatitis

GGT levels are also elevated in acute and chronic pancreatitis.

GGT in CSF

Lactate dehydrogenase (LDH), creatine kinase (CK) and GGT in CSF and serum were studied in 25 cases of meningitis of which 10 were tuberculous meningitis (TBM) and 15 were pyogenic meningitis (PM) and equal control subjects and concluded that GGT, CK and LDH were significantly elevated in cases of meningitis. It was not possible to differentiate the type of meningitis on the basis of enzymatic activity, however it was possible to predict prognosis because higher basal activity and serial rise were associated with poor prognosis of all the enzymes. CSF GGT levels correlated best with the clinical picture.[2]

In a study aspartate transaminase (AST), LDH, GGT and creatine phosphokinase (CPK) and creatine kinase brain isomer (CKBB) were studied in CSF on 16 patients with aseptic meningitis, 25 with PM and 15 with meningism and concluded that GGT levels were raised in PM and has prognostic value.[53]

There were other studies which suggested that there is a rise of CSF GGT in meningitis and it could be of diagnostic and/or prognostic value.[54,55]

The GGT in CSF can be measured by two methods namely;

1. International Federation of Clinical Chemistry (IFCC)[56]
2. Persijin and Vander method.[57]

Treatment

Early treatment should be the goal in meningitis to prevent mortality and morbidity. This includes;

General measures;

- Complete bed rest
- Maintenance of nutrition, fluid and electrolytes.
- Maintenance of vital functions.
- Prevention of bed sores, bowel and bladder care if the patient is in altered sensorium and or has neurodeficits.

- Symptomatic treatment like control of seizures, reduction of cerebral oedema, treatment of secondary infections.

Specific measures

This depends on the etiology of meningitis like antibiotics for bacterial meningitis, antituberculous treatment for tuberculous meningitis and antifungals for fungal meningitis and adjunctive therapy like steroids.

Prognosis

In general the risk of death from bacterial meningitis increases with decreased level of consciousness on admission, onset of seizures within 24 hours of admission, signs of raised ICP, young age (infancy) and age more than 50 years, the presence of co-morbid conditions including shock and / need for mechanical ventilation and delay in initiation of treatment. Decreased CSF glucose concentration less than 40 mg/dl and markedly increased CSF protein more than 300 mg/dl have been predictive of increased mortality and poorer outcomes in some studies.[2]

In a study it was revealed that the following risk factors were associated with poor prognosis – duration of fever more than 10 days, abnormal cranial imaging, initial serum CRP more than 16 mg/dL, initial CSF glucose less than 12 mg/dL, initial CSF LDH more than 220 IU/L, streptococcus pneumoniae infection. In order to improve the prognosis of bacterial meningitis, factors associated with poor prognosis should be recognized at early stage of the illness.[58]

METHODOLOGY

The present study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on patients with meningitis.

Study design

One year cross sectional study.

Study period

The present study was conducted during January 2007 to December 2007.

Method of collection of data

Source of Data

Patients presenting with symptoms and signs suggestive of meningitis and undergoing CSF analysis in KLES Dr. Prabhakar Kore Hospital and MRC Belgaum formed the material for the study.

Sample size

A sample size of 40 cases were calculated on the basis of statistical software considering $\alpha = 0.05$ and $\beta = 80\%$.

Sampling procedure

80% of, average number of similar cases admitted to KLES Dr. Prabhakar Kore Hospital Belgaum over a period of last three years were considered to calculate ideal number of sample size.

Age and sex matched 10 individuals without any evidence of neurological disease served as controls. These patients had minor surgical ailments like hernia or hydrocoele and were operated under spinal anaesthesia (SA) and CSF samples were taken at that time.

Selection criteria

Inclusion Criteria

- Patients admitted within five days of onset of symptoms of meningitis.
- Pyogenic and tuberculous meningitis cases only.
- Patients aged above 14 years.

Exclusion Criteria

- Patients who had received antibiotics or antitubercular treatment outside.
- Patients having symptoms of meningitis for more than five days.
- Patients suffering form hepatobiliary disorders, alcoholism, other neurological disorders like head injury, stroke, and meningitis of viral, fungal or protozoal etiology.
- Patients receiving following drugs – warfarin, phenytoin, phenobarbital.

Procedure

Patients attending to the out patients department of Medicine and Neuromedicine at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum with meningitis were evaluated and selected by detailed medical history and physical examination. The study was approved by the Ethical and Research Committee of Jawaharlal Nehru Medical College, Belgaum.

After finding the suitability as per inclusion and exclusion criteria they were selected for the study and briefed about the nature of the study, the interventions used and written informed consent was obtained (Annexure–I). The consented patients were enrolled in the present study. Further, descriptive data of the participants like name, age, sex, detailed history, were obtained by interviewing the participants and clinical examination and necessary investigations were recorded on predesigned and pretested proforma (Annexure-II).

CSF evaluation was done by lumbar puncture using 20 or 22 G spinal needle on day one and day five. Day one means day of admission in the hospital and day five means fifth day of admission. The duration of follow-up was limited to the hospital stay.

Analysis of Diagnosis

Detailed history was obtained regarding fever, headache, vomiting and neck pain and any source of infection like cough with expectoration and ear discharge. Clinical examination of each case was done looking for signs of meningeal irritation, fever, vital signs, any focal neurological deficits and any focus of infection. Fundus examination was done and if there was no risk of herniation on the clinical examination, a CSF evaluation was done immediately.

The following investigations were done on these patients.

CSF

- Protein, sugar, ADA levels.
- Cell count, cell type.
- Gram's stain, acid fast bacilli (AFB), India-ink.
- Culture.
- GGT.

Blood

- Hemoglobin %.
- Total and differential white blood cell count.
- Erythrocyte sedimentation rate (ESR).
- Random blood sugar.
- Liver function tests.

Chest X-ray

Neuroimaging

- CT or MRI

Symptoms and signs related investigations like fine needle aspiration cytolocy (FNAC) of lymph nodes, Gram's staining, AFB staining and culture of discharging focus.

Criteria for diagnosis of meningitis (All may not be present in each patient)

Clinical

- Triad of fever, headache and nuchal rigidity.
- Alteration in mental status.
- Nausea, vomiting, photophobia.
- Seizures
- Signs of meningeal irritation like neck stiffness, Kernig's sign and Brudzinski's neck and leg signs.

Laboratory

CSF Examination

- Pleocytosis.
- Raised protein content.
- Microscopy showing the causative organism.
- Culture growing the organism.
- Raised ADA levels.

Neuroimaging

- Diffuse meningeal enhancement on CT / MRI.

Criteria for diagnosing different types of meningitis (All may not be present in every patient)

Group I (Tuberculous meningitis)

1. Clinical

    a. Usually insidious in onset.
    b. May be associated with tuberculosis (TB) of other organs for example pulmonary tuberculosis, TB lymphadenitis, abdominal tuberculosis.
    c. Signs of meningeal irritation.

2. Laboratory

    a. CSF analysis
        i. Pleocytosis of more than 10 cells per cubic millimeter, predominantly lymphocytes.
        ii. Proteins more than 45 mg/dL.
        iii. Sugar less than 40 mg/dL or less than 40% of the blood glucose concentration.
        iv. Ziehl – Neelsen (Z-N) stain may be positive for acid fast bacilli.
        v. Positive culture for AFB
        vi. ADA more than 10 U/L.
    b. Neuroimaging: May show meningeal enhancement, basal exudates and / or tuberculoma.

Group II (Pyogenic meningitis)

1. Clinical
    a. Usually acute in onset
    b. May be associated with sinusitis, otitis media.
    c. Signs of meningeal irritation.

2. Laboratory
    a. CSF analysis
        i. Pleocytosis, usually more than 250 cells per cubic millimeter, predominantly neutrophils.
        ii. Proteins more than 45 mg/dL.
        iii. Sugar less than 40 mg/dL or less than 40% of the blood glucose concentration.
        iv. Gram's stain may show gram positive or gram negative organisms.
        v. Culture may grow the causative organism.
    b. Neuroimaging: May show diffuse meningeal enhancement abscesses or parameningeal focus.

Group III (Viral Meningitis)

1. Clinical
    a. Usually acute in onset.
    b. Signs of meningeal irritation

2. Laboratory

   a. CSF analysis

      i. Pleocytosis of more than 10 cells per cubic millimeter, predominantly lymphocytes.
      ii. Proteins more than 45 mg/dL.
      iii. Sugar normal.
      iv. PCR may be positive for the DNA or RNA of the causative virus.

   b. Neuroimaging: May show diffuse meningeal enhancement.

Group IV (Toxoplasma meningitis)

1. Clinical
   a. Usually insidious in onset.
   b. Usually associated with HIV infection.
   c. Signs of meningeal irritation.

2. Laboratory

   a. CSF Analysis

      i. Pleocytosis of more than 10 cells per cubic millimeter, predominantly mononuclear cells.
      ii. Proteins more than 45 mg/dl.
      iii. Sugar normal or decreased.
      iv. CSF sediment may show the organisms.

v. Immunoglobulin M indirect fluorescent antibody titre may be positive.

b. Neuroimaging: Usually shows multiple nodular or ring – enhancing brain lesions.

Group V (Cryptococcal meningitis)

1. Clinical
    a. Usually insidious in onset.
    b. Usually associated with HIV infection.
    c. Signs of meningeal irritation.

2. Laboratory
    a. CSF analysis
        i. Variable pleocytosis, predominantly lymphocytic.
        ii. Proteins more than 45 mg/dL.
        iii. Sugar less than 40 mg/dl or less than 40% of the blood glucose concentration.
        iv. India ink preparation is distinctive and diagnostic.
        v. Latex agglutination test for the cryptococcal polysaccharide antigen gives rapid results.
        vi. The organism may be grown in fungal cultures.
    b. Neuroimaging: May show diffuse meningeal enhancement or a solitary cryptococcoma.

Estimation of GGT in CSF [56, 57]

Performed by testing the GGT level in CSF by IFCC recommended method using γ-glutamyl–3 carboxy 4-nitranilide (GCNA) and glycylglycine as substrates.[47,48]

Principle

Gamma glutamyl transferase catalyzes the transfer of the glutamyl moiety form GCNA to glycylglycine thereby releasing 5-amino-2-nitrobenzoate which absorbs at 405 nm. This change is proportional to the γ-glutamyl transferase activity and is measured using a bichromatic (405, 600nm) rate technique.

$$\text{GCNA+ glycylglycine} \xrightarrow{\text{GGT}} \alpha\text{-}\gamma\text{-glutamyl glycylglycine + 5-amino-2-nitrobenzoate.}$$

Reagents

- Wells 1 to 6 - GCNA 0.69 mg
- Wells 7 to 8 - Glycylglycine 90 mM/L

Reagent preparation

- Mixing and diluting are automatically performed by the instrument
- Storage 2 to 8˚C

Procedure

The GGT flex reagent cartridge, Cat No DFUSA is required to perform the GGT test.

The sampling, reagent delivery, mixing, processing and printing of results are automatically performed.

Sample size	32 µL (15µL)
Reagent volume	75 µL
Diluent volume	313 µL
Test temperature	37˚C
Wavelength	405 and 600 nm
Type of measurement	Bichromatic rate.

Verification

The following information should be considered when verifying the γ-glutamyl transferase method.

Assay Range (37˚C)	0-800 U/L
Reference material	Secondary verifiers such as enzyme verifier (Cat No.DC19)
Suggested verification levels	70, 400, 700 IU/L
Verification scheme	Three levels in triplicate
Verification frequency	Every new reagent cartridge lot. Every three months for any one lot

Assigned coefficients	Standard sample size = 32µL
	C_0 - 1.000
	C_1 3.360
	Alternate sample size = 15µL
	C_0 - 8.000
	C_1 7.230

Results

The instrument automatically calculates and prints the concentration of γ glutamyl transferase in IU/L.

Reference interval at 37°C in serum

Females - 5 – 55 IU/L

Males - 15-85 IU/L

Statistical analysis

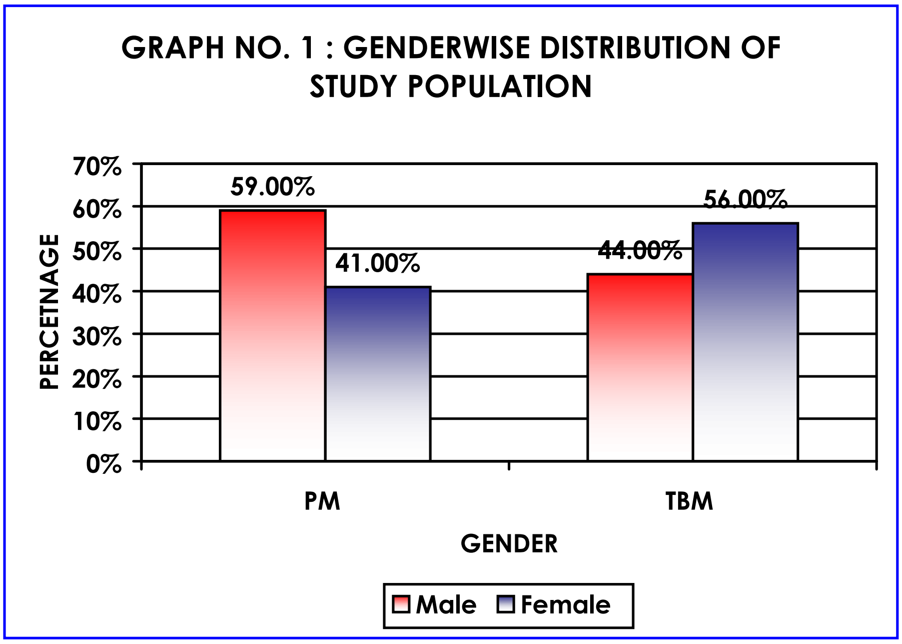
The data obtained was analysed using students paired 't' test for comparison of GGT levels on day one and day five in each group. Students unpaired 't' test was used to compare the value of GGT among the two groups.

RESULTS

The present study was conducted in the Department of Medicine, KLES Dr. Prabharkar Kore Hospital and Medical Research Centre, Belgaum and the findings obtained are tabulated as below.

Table No. 1: Genderwise distribution of study population

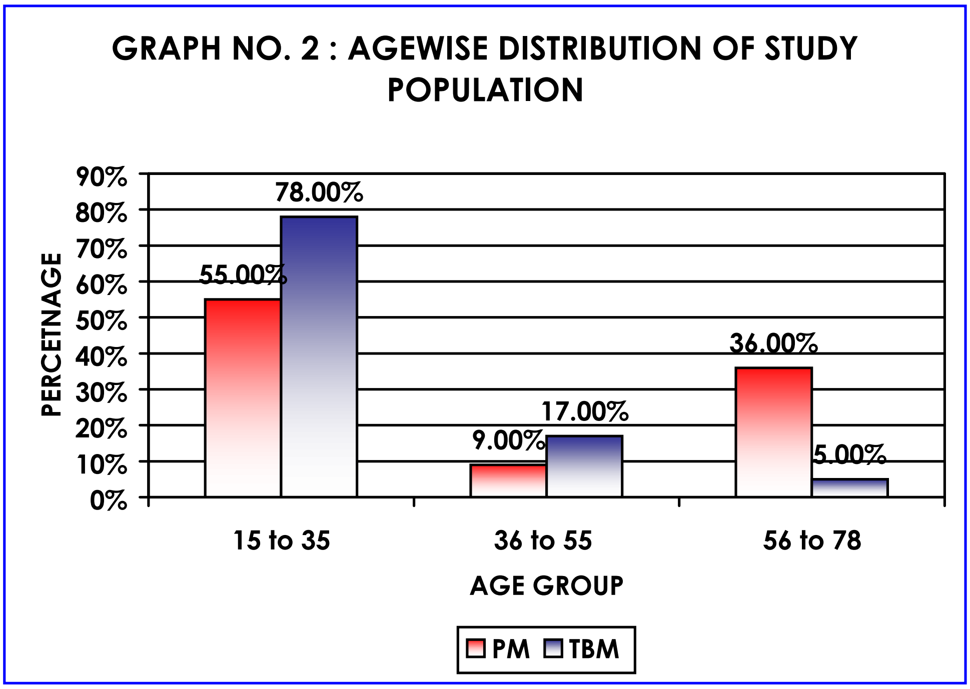
Gender	Cases (n=40)						Controls (n=10)	
	PM (n=22)		TBM (n=18)		Total (n=40)			
	No	%	No	%	No.	%	No	%
Male	13	59.0%	08	44.0%	21	52.5%	07	70.0%
Female	09	41.0%	10	56.0%	19	47.5%	03	30.0%



In the present study there were 59.0% males and 41.0% females in pyogenic meningitis. In tuberculous meningitis 44.0% were males and 56.0% were females.

Table No. 2: Agewise distribution of study population

Age (Years)	Cases						Controls (n=10)	
	PM (n=22)		TBM (n=18)		Total (n=40)			
	No	%	No	%	No.	%	No	%
15 to 35	12	55.0%	14	78.0%	26	65.0%	05	50.0%
36 to 55	02	9.0%	03	17.0%	05	12.5%	04	40.0%
56 to 78	08	36.0%	01	5.0%	09	22.0%	01	10.0%



In the present study the pyogenic meningitis group had 55% patients in the age group of 15 to 35 years, nine percent in 36 to 55 years and 36% in 56 to 78 years. Similarly, in tuberculous meningitis there were 78% in 15 to 35 years, 17% in 36 to 55 years and five percent in 56 to 78 years group. The control group had 50% in 15 to 35years, 40% in 36 to 55 years group and 10% in 56 to 78 years group.

Table No. 3: Incidence of symptoms

Symptoms	PM (n=22)		TBM (n=18)		Total (n=40)	
	No	%	No.	%	No	%
Headache	20	91.0%	18	100.0%	38	95.0%
Fever	20	91.0%	15	83.0%	35	87.5%
Altered Sensorium	18	82.0%	10	56.0%	28	70.0%
Vomiting	14	64.0%	09	50.0%	23	57.5%
Neuro-deficits	09	41.0%	04	22.0%	13	32.5%
Convulsions	04	18.0%	01	6.0%	05	12.5%

In the present study, headache (91% in PM and 100% in TBM) was commonest presentation followed by fever (91% in PM and 83% in TBM), altered sensorium (82% in PM and 56% in TBM), vomiting (64% in PM and 50% in TBM), neurodeficits (41% in PM and 22% in TBM) and the least common was convulsions (18% in PM and six percent in TBM).

Table No. 4: Neurological deficits

Neurodeficits	PM (n=22)		TBM (n=18)		Total (n=40)	
	No.	%	No	%	No	%
III CN Palsy	00	0.0%	01	6.0%	01	2.5%
VI CN Palsy	05	23.0%	03	17.0%	08	20.0%
VII CN Palsy	03	14.0%	02	11.0%	05	12.5%
IX, X CN Palsy	00	0.0%	01	6.0%	01	2.5%
Hemiplegia	03	14.0%	02	11.0%	05	12.5%

In the present study the neurodeficits in pyogenic meningitis group were sixth cranial nerve palsy (23%), seventh cranial nerve palsy (14%) and hemiplegia (14%). In tuberculous meningitis the neurodeficits were third cranial nerve palsy (six percent), sixth cranial nerve palsy (17%), seventh cranial nerve palsy (11%), ninth, tenth cranial nerves palsy (six percent) and hemiplegia (11%). Among the neurodeficits sixth cranial nerve palsy was commonest.

Table No 5: Signs of meningeal irritation

Signs of meningeal irritation	PM (n=22)		TBM (n=18)		Total (n=40)	
	No.	%	No	%	No	%
Neck rigidy	21	96.0%	18	100.0%	39	97.5%
Kernig’s sign	10	46.0%	06	33.0%	16	40.0%
Brudzinski’s neck sign	02	2.0%	01	6.0%	03	7.5%
Brudzinski’s leg sign	00	0.0%	01	6.0%	01	2.5%

In the present study the signs of meningeal irritation were present in majority of the cases in both the groups. In pyogenic meningitis, neck rigidity was present in 96%, Kernig’s sign in 46%, Brudzinski’s neck sign in two percent and none had Brudzinski’s leg sign. Similarly in tuberculous meningitis neck rigidity was present in all cases, Kernig’s sign in 33%, Brudzinski’s neck sign in six percent and Brudzinski’s leg sign in six percent cases.

Table No. 6: CSF cell count

Cell count (mm^3)	PM (n=22)		TBM (n=18)		Total (n=40)	
	No.	%	No	%	No	%
0 to 100	03	13.0%	14	78.0%	17	42.5%
101 to 300	14	64.0%	04	22.0%	18	45.0%
More than 300	05	23.0%	00	0.0%	05	12.5%

In the present study, all the cases had elevated CSF cell count. The cell count varied between 32 to 258 cells/mm^3 in tuberculous meningitis. Majority (78%) of the patients with tuberculous meningitis had a cell count of less than 100 cells/mm^3, 22% had cells in the range of 101 to 300 cells/mm^3. In pyogenic meningitis, the cell count varied between 56 to 1000 cells/mm^3 and in majority (64%) it was in the range of 101 to 300 cells/mm^3, 14% had less than 100 cells/mm^3 and 24% had more than 300 cells/mm^3.

Table No. 7: Predominant cell type in the CSF

Cell type	PM (n=22)		TBM (n=18)		Total (n=40)	
	No.	%	No	%	No	%
Neutrophils	22	100.0%	00	0.0%	22	55.0%
Lymphocytes	00	0.0%	18	100.0%	18	45.0%

In the present study, all patients of tuberculous meningitis had lymphocytes as the predominant cells in their CSF and all patients with pyogenic meningitis had a neutrophilic response in their CSF.

Table No. 8: CSF Protein

CSF Protein (mg/dL)	PM (n=22)		TBM (n=18)		Total (n=40)	
	No.	%	No	%	No	%
45 to 100	09	41.0%	09	50.0%	18	45.0%
101 to 300	12	55.0%	08	44.0%	20	50.0%
301 to 600	01	4.0%	00	0.0%	01	2.5%
More than 600	00	0.0%	01	6.0%	01	2.5%

In the present study, the CSF protein levels were elevated in all cases and varied between 68 to 1020 mg%. The majority of the tuberculous meningitis (94%) and pyogenic meningitis (96%) had CSF protein in the range of 45 to 300 mg%. But the very high level more than 600 mg% is seen only in tuberculous meningitis.

Table No. 9: CSF Sugar

CSF Sugar (mg/dL)	PM (n=22)		TBM (n=18)		Total (n=40)	
	No.	%	No	%	No	%
Less than or equal to 30	18	82.0%	06	33.0%	24	60.0%
30 to 40	02	9.0%	11	61.0%	13	32.5%
More than 40	02	9.0%	01	6.0%	03	7.5%

In pyogenic meningitis 20 (91%) cases had reduced CSF sugars, and majority (82%) had severe reduction, that is less than 30 mg%. In tuberculous meningitis, CSF sugar level was reduced in 17 (94%) cases, but most (61%) had mild reduction that is in the range of 30 to 40 mg%.

Table No. 10: CSF microbiology

Microbiology of CSF	PM (n=22)		TBM (n=18)		Total (n=40)	
	No.	%	No	%	No	%
Positive Gram stain/ AFB	10	45.0%	00	0.0%	10	25.0%
Positive culture	21	95.0%	01	6.0%	22	55.0%

In the present study, Gram stain showed organisms in 10(45%) cases of pyogenic meningitis compared to 21 (95%) cases with culture positiveness. In tuberculous meningitis the smear was negative for AFB in all the cases, and there was growth of mycobacterium tuberculosis in one (six percent) patient.

Table No. 11: Blood culture positive cases and the organisms grown

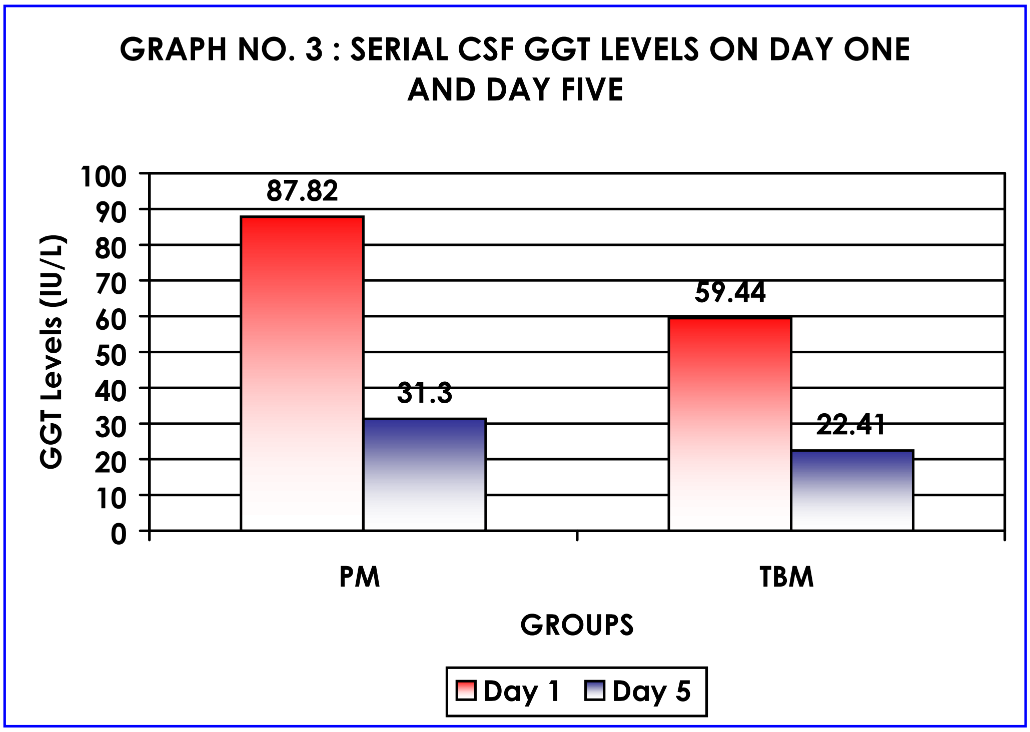
Organisms	Cases	
	Number	Percentage
Streptococcus pneumoniae	11	50.0%
Klebsiella pneumoniae	04	18.0%
Streptococcus pyogenes	02	9.0%
Escherichia Coli	01	5.0%
Staphylococcus aureus	01	5.0%
Nisseria meningitidis	01	5.0%
Listeria monocytogenes	01	5.0%
Mycobacterium tuberculosis	01	5.0%

In the present study, culture was positive in 95% of pyogenic meningitis and six percent of tuberculous meningitis. In pyogenic meningitis the most common organism isolated was streptococcus pneumoniae (50%), followed by klebsiella pneumoniae (18%), streptococcus pyogenes (nine percent), E. coli (five percent), staphylococcus aureus (five percent), N. meningitidis (five percent), L. monocytogenes (five percent). There was only one positive culture in TBM group.

Table No. 12: Serial CSF GGT on day one and five

CSF GGT (IU/L)	Total (n=40)	PM (n=22)		TBM (n=18)		p value PM:TBM
		Mean	S.D.	Mean	S.D.	
Day one	75	87.82	36.16	59.44	35.71	0.017*
Day five	27	31.30	29.83	22.41	29.08	0.36

$^*p \le 0.05$ Statistically significant



It was found that CSF GGT was raised to a higher level on day one (mean of 87.82 in PM and 59.44 in TBM) compared to day five (mean of 31.3 in PM and 22.41 in TBM) in both the groups. There is a statistical significance in CSF GGT levels between PM and TBM group on day one, as the levels were much higher in pyogenic group.

Table No. 13: CSF GGT levels in control group

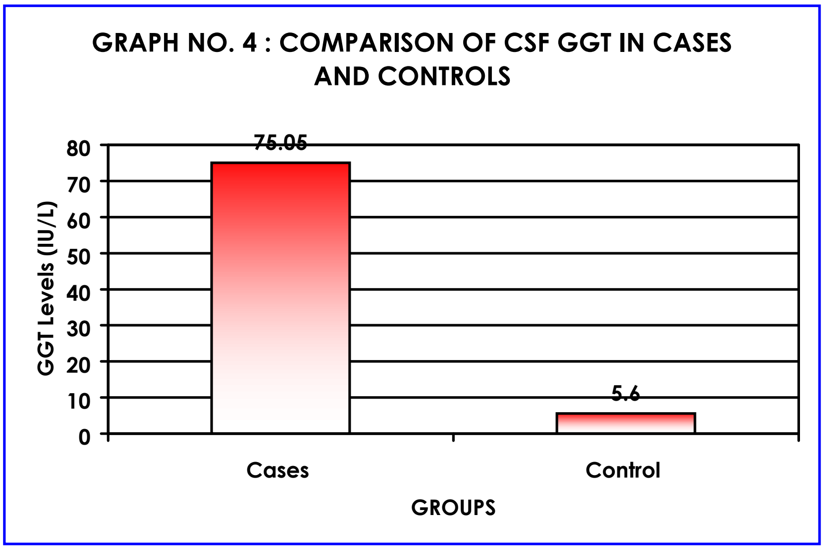
Controls	CSF GGT levels (IU/L)	
	Mean	**S.D.**
Male	5.14	1.95
Female	6.67	1.15
Total	5.60	1.84

The range of CSF GGT in controls undergoing minor surgeries was in the range of 4 to 8 IU/L. It was 5.14±1.95 in males and 6.67±1.15 in females.

Table No. 14: Comparison of CSF GGT in cases and controls

CSF	Cases		Controls		p value
	Mean	**S.D.**	**Mean**	**S.D.**	
GGT IU/L	75.05	38.27	5.60	1.84	0.001**

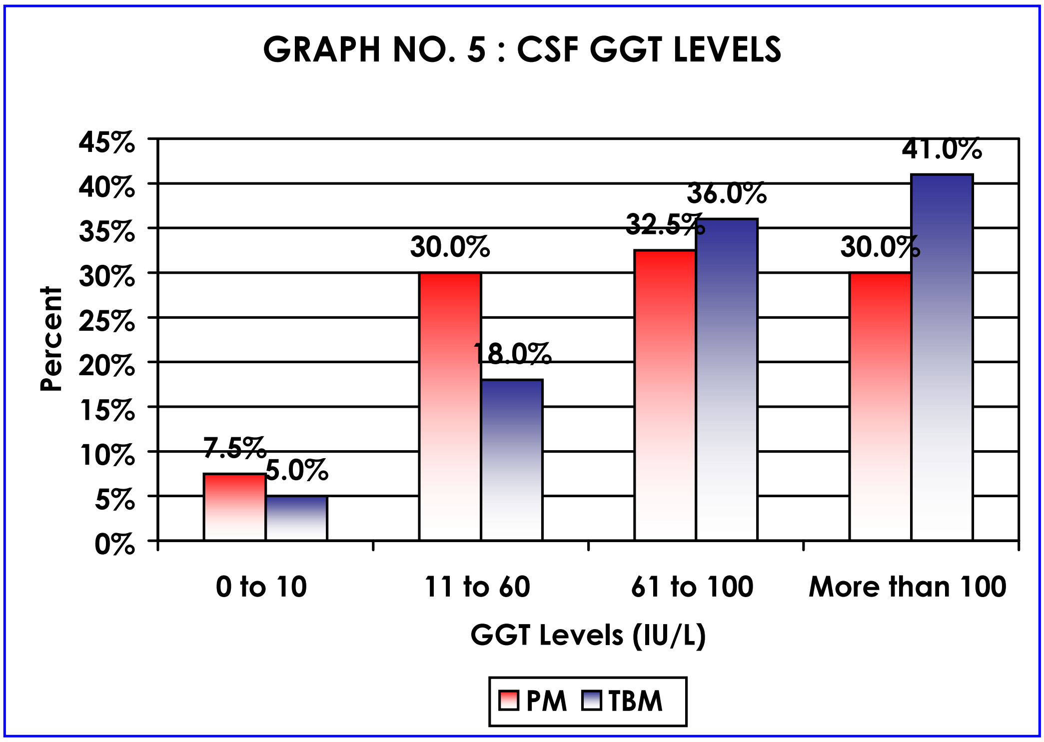
** $p \leq 0.001$ Statistically highly significant



In the present study CSF GGT was raised in all the cases with a mean level of 75.05 IU/L on day one compared to 5.6 IU/L in controls. The raise was highly significant statistically.

Table No. 15: CSF GGT levels

CSF GGT level IU/L	PM (n=22)		TBM (n=18)		Total (n =40)	
	No	%	No	%	No	%
0 to 10	01	7.5%	02	5.0%	03	11.0%
11 to 60	04	30.0%	08	18.0%	12	44.0%
61 to 100	08	32.5%	05	36.0%	13	28.0%
More than 100	09	30.0%	03	41.0%	12	17.0%



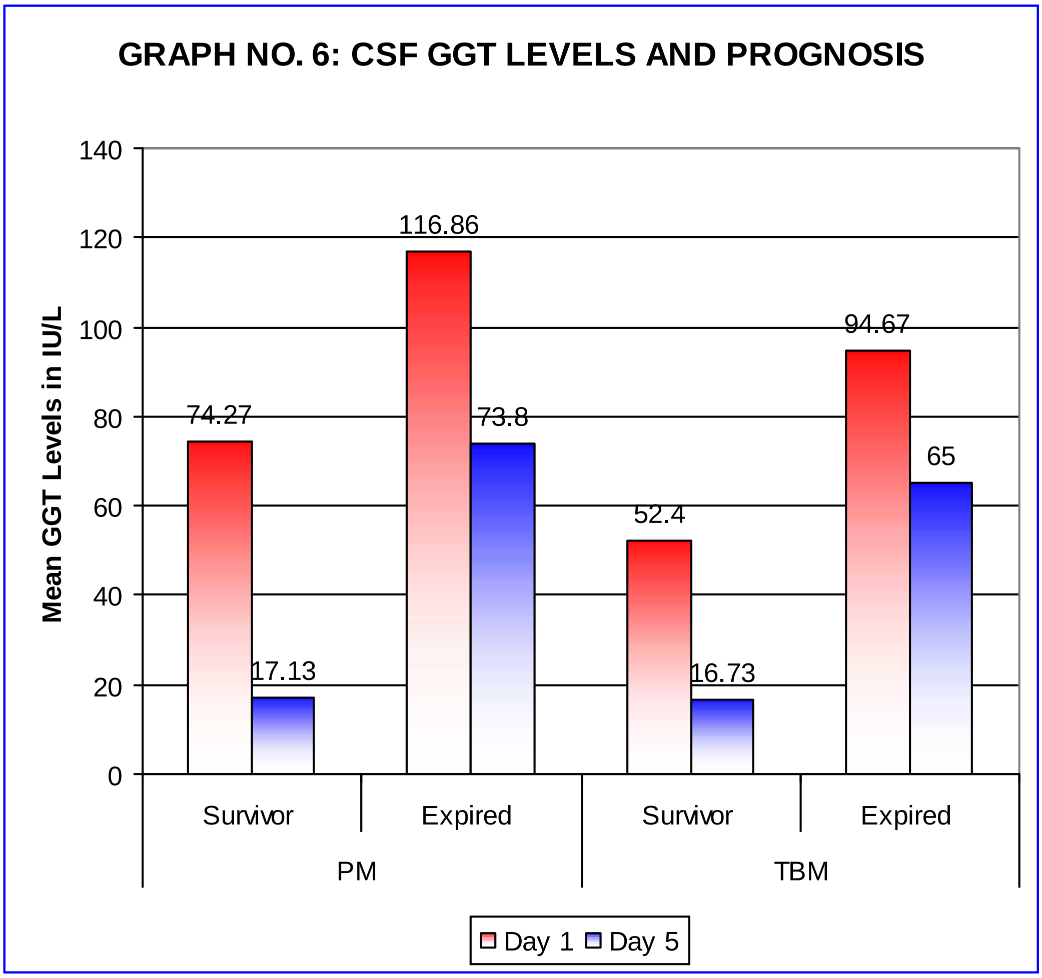
In the present study the moderate raise of GGT was more common in TBM cases compared to severe raise in PM cases but was not statistically significant. The p value using Chi square test was 0.17, indicating that there is no association of the different levels of GGT in the two groups of cases.

Table No. 16: CSF GGT levels and prognosis

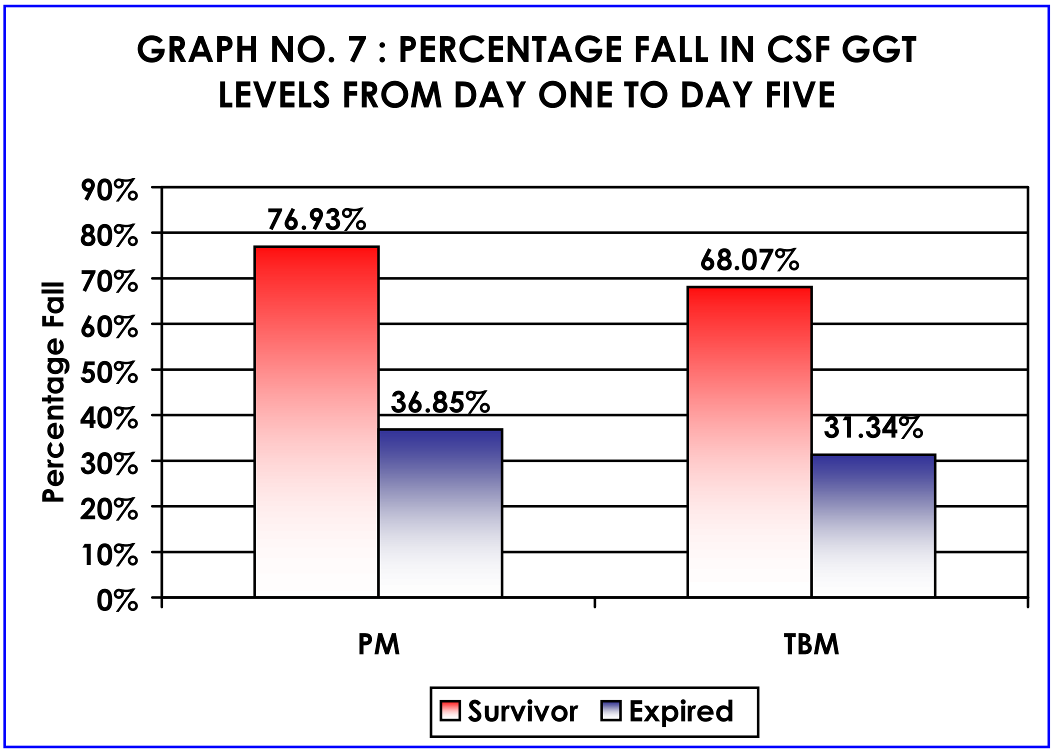
Prognosis			Day 1	Day 5	% Reduction
PM (n=22)	**Survivor (n=15)**	**Mean**	74.27	17.13	76.93
		S.D.	35.79	13.51	
	Expired (n=7)	**Mean**	116.86	73.80	36.85
		S.D.	12.10	24.02	
	p value		0.006*	< 0.001**	-
TBM (n=18)	**Survivor (n=15)**	**Mean**	52.40	16.73	68.07
		S.D.	31.49	15.50	
	Expired (n=3)	**Mean**	94.67	65.00	31.34
		S.D.	40.81	77.78	
	p value		0.05*	0.021*	-
Total (n=40)	**Survivor (n=30)**	**Mean**	63.33	16.93	-
		S.D.	34.94	14.29	
	Expired (n=10)	**Mean**	110.20	71.29	-
		S.D.	24.14	37.57	
	p value		< 0.000**	< 0.000**	-

* $p \leq 0.05$ Statistically significant

** $p \leq 0.001$ Statistically highly significant



In the present study the day one GGT level was much higher in cases who expired compared to survivors in both PM and TBM with a statistically significant p value. The levels were persistently higher on day five in both groups with a significant p value.

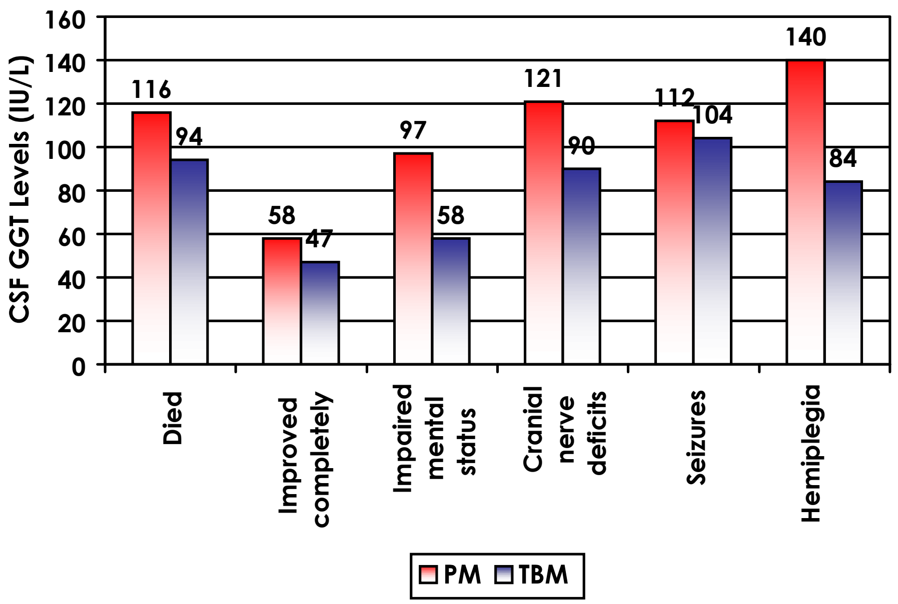


The percentage fall in the expired patients compared to those who survived in both the groups is less than 50% which is apparently significant. But the test to confirm significant fall could not be conducted because in expired patients on day five the values were few, which is not a sizable number to conduct the test.

Table No. 17: CSF GGT levels and clinical outcome

Microbiology of CSF	PM		TBM		Total	
	No.	GGT	No.	No.	GGT	GGT
Died	07	116	03	94	10	110
Improved completely	10	58	11	47	21	50
Impaired mental status	03	97	02	58	05	81
Cranial nerve deficits	02	121	03	90	05	102
Seizures	04	112	01	104	05	114
Hemiplegia	01	140	02	84	03	102

GRAPH NO. 8: CSF GGT LEVELS AND CLINIAL OUTCOME



The CSF GGT was much higher in patients who had poor clinical outcome compared to those who improved completely**.** The number of cases in each group other than those died was not adequate to compare statistically.

Table No 18: Other prognostic marker and GGT levels

Prognostic marker	PM			TBM			Total	
	Surv. (n=15)	Exp. (n=7)	p value	Surv. (n=15)	Exp. (n=3)	p value	Surv. (n=30)	Exp. (n=10)
Day 1 GGT	78	116	0.006*	52	94	0.05*	65	110
Day 5 GGT	17	73	0.001**	16	65	0.021*	16	71
Altered sensorim at admission	11	7	0.131	7	3	0.093	18	10
Seizures within 24hrs of admission	2	2	0.388	0	1	0.021*	2	3
Sign of raised ICP	6	7	0.008*	5	2	0.280	11	9
Age > 50 yrs (n = 9)	4	4	0.343	1	0	0.343	5	4
Shock (n= 5)	1	3	0.576	0	1	0.576	1	4
Ventilatory support (n=7)	1	3	0.809	1	2	0.809	2	5
CSF sugar < 40 mg%	13	6	0.952	10	3	0.239	23	9
CSF protein > 300 mg%	0	1	0.083	2	0	0.083	2	1

* $p \leq 0.05$ Statistically significant
** $p \leq 0.001$ Statistically highly significant

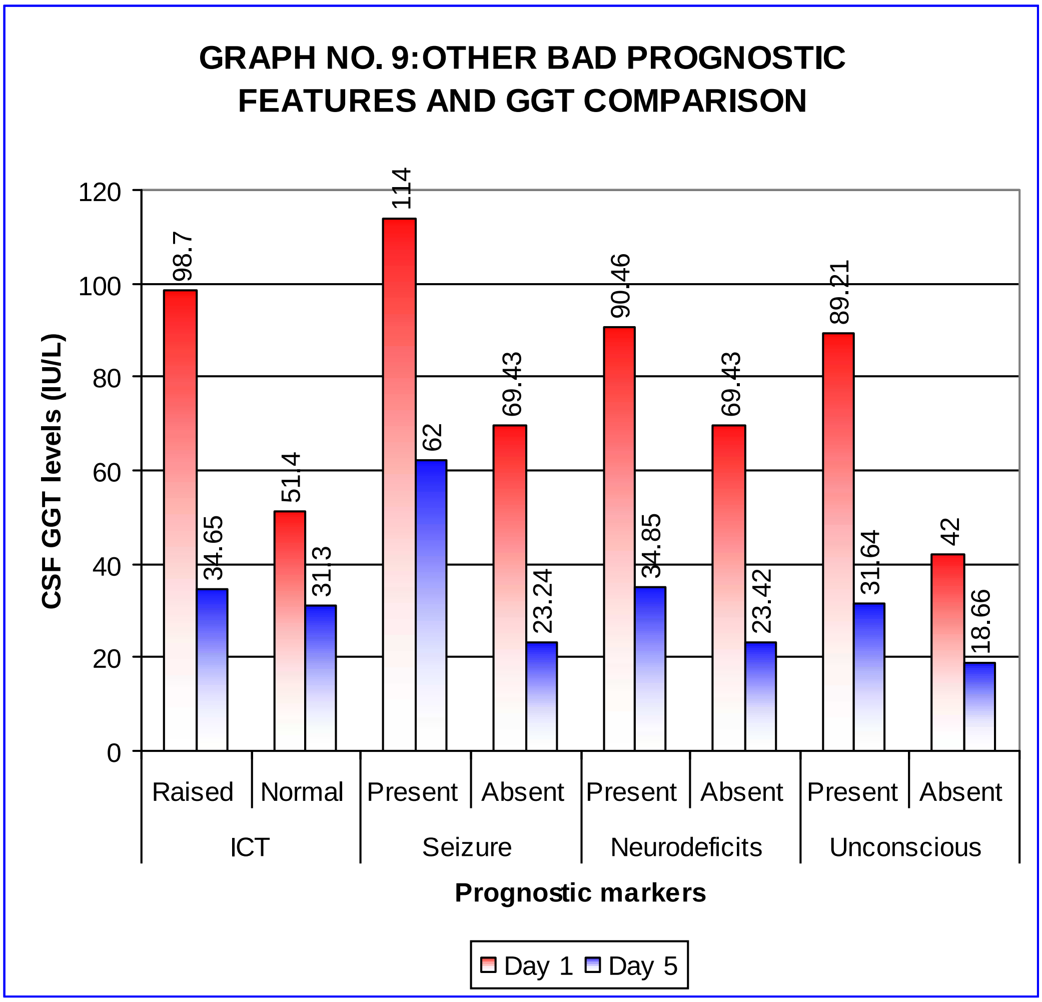
In this study, the CSF GGT was compared to other clinical and laboratory prognostic markers. The sample was not adequate in each group except CSF GGT to calculate statistical significance, but however the tests are conducted with the available values. Compared to the other clinical and laboratory prognostic markers, CSF GGT on day one and five were the best predictors of prognosis with a statistical significance. Among the others, seizures (in TBM) and raised ICP (in PM) were the only other statistically significant predictors in this study.

Table No 19: Other bad prognostic features and GGT comparison

GGT			Raised ICP	Seizures	Neurodeficits	Unconscious
Day 1	**Present**	**n**	20	05	27	28
		Mean	98.70	114.00	90.46	89.21
		S.D.	30.12	24.31	30.12	31.80
	Absent	**n**	20	35	13	12
		Mean	51.40	69.43	69.43	42.00
		S.D.	30.35	36.75	36.75	31.74
	p value		0.000**	0.012*	0.076	0.000**
Day 5	**Present**	**n**	20	05	27	28
		Mean	34.65	62.00	34.85	31.64
		S.D.	35.44	56.87	38.14	31.89
	Absent	**n**	20	35	13	12
		Mean	21.30	23.24	23.42	18.66
		S.D.	21.86	22.19	23.09	21.40
	p value		0.167	0.010*	0.262	0.211

* $p \leq 0.05$ Statistically significant

** $p \leq 0.001$ Statistically highly significant



In the present study CSF GGT levels were compared to other clinical features which are suggestive of bad prognosis, it was seen that raised ICT on day one, seizures on day one and five, unconsciousness on day one have statistically significant correlation.

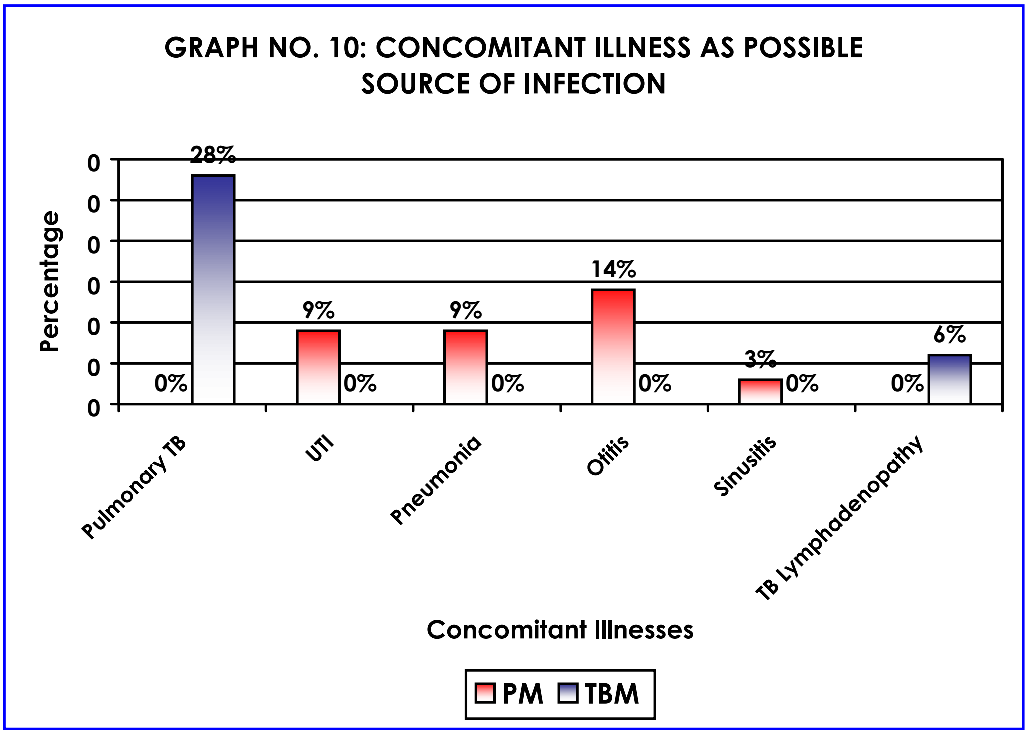
Table No 20: ESR in meningitis

ESR (mm at one hour)	PM (n=22)		TBM (n=18)		Total (n=40)	
	No.	%	No.	%	No.	%
0 to 20	21	96.0%	00	0.0%	21	52.5%
21 to 40	01	4.0%	05	28.0%	06	15.0%
41 to 60	00	0.0%	06	33.0%	06	15.0%
More than 60	00	0.0%	07	39.0%	07	17.5%

All the patients with tuberculous meningitis had raised ESR, 28% had ESR 21 to 40, 33% had 41 to 60 and 39% had more than 60 mm at the end of one hour. Majority (96%) patients with pyogenic meningitis had ESR less than 20 mm at the end of one hour.

Table No 21: Concomitant illness as possible source of infection

Illness	PM (n=22)		TBM (n=18)		Total (n=40)	
	No.	%	No.	%	No.	%
Pulmonary TB	00	0.0%	05	28.0%	05	12.5%
Urinary tract infection(UTI)	02	9.0%	00	0.0%	02	5.0%
Pneumonia	02	9.0%	00	0.0%	02	5.0%
Otitis	03	14.0%	00	0.0%	03	7.5%
Sinusitis	03	3.0%	00	0.0%	03	7.5%
Tuberculous Lymphadenopathy	00	0.0%	01	6.0%	01	2.5%



In the present study 34% of TBM cases were associated with tuberculosis in other organs, more so in lungs (28%). And a total of 64% of PM cases had a detectable source of infection like otitis (14%), UTI (nine percent), pneumonia (nine percent) and sinusitis (three percent).

HIV and CSF GGT

All the patients included in the study were HIV negative, it helped in removing one confounding factor as HIV itself can lead to low grade inflammation of brain parenchyma and meninges and leads to raised CSF GGT levels.

CSF ADA

CSF ADA was more than 10 U/L in all the cases of tuberculous meningitis and was less than 10 in all the cases of pyogenic meningitis.

India Ink

CSF of all the patients were processed with India Ink to rule out cryptococcal meningitis.

Neuroimaging

Neuroimaging was performed in all the cases. (either CT or MRI). CT was performed in 34 cases and MRI in 6 cases. CT scan brain plain was normal in 18 cases, nine cases were showing cerebral edema and sinustitis in three cases, mastoiditis in one, cortical venous thrombosis (CVT) in one and infarction in two cases. MRI was normal in two cases, suggested cerebral edema in one, infarction in two and CVT in one case.

Chest X-ray

Chest X-Ray was done in all the patients. It was normal in 28 patients. In the tuberculosis group six (33%) patients had X-Ray suggestive of pulmonary tuberculosis. In pygenic meningitis group five patients had abnormal x-rays, out of which two had lobar pneumonia and three had aspiration pneumonia.

Other cultures

Other cultures from body fluid or discharge / secretion were positive in seven cases in total, (two urine, two sputum, two ear discharges and one blood culture).

Tuberculosis evidence elsewhere

Spatum for AFB was positive in four cases and one case had cervical lymphadenopathy where FNAC revealed caseous necrosis.

Outcome

Ten (25%) out of total 40 cases of meningitis had expired and one (2.5%) remained same. Out of the 10 expired cases, seven were in pyogenic meningitis group and three were in tuberculosis meningitis group, suggesting that mortality was higher in pyogenic meningitis group.

DISCUSSION

The present study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on patients with meningitis.

We began this endeavour with two simple objectives. One, of course, was to estimate CSF GGT levels serially on day one and day five of admission in patients with pyogenic and tuberculous meningitis and other being to see whether GGT levels have prognostic significance in cases of tuberculous and pyogenic meningitis.

A review of literature had shown us that CSF GGT could have prognostic value in tuberculous and pyogenic meningitis.[2] Over the last decade or so, various investigators have shown us that GGT in CSF is raised in meningitis and could have significant prognostic value.[2,53] However the emphasis was on multiple enzyme levels in CSF and were unable to depict the prognosis on the basis of one prognostic marker with consensus guidelines. Only one study in the past had tried evaluating the enzymes in CSF serially in India.[2] It revealed a significant prognostic value in both tuberculous and pyogenic meningitis. Hence, we embarked on this endeavour.

Cost constraints and unavailability prevented us from doing PCR for mycobacterium. However, we achieved our objectives of getting a quick and reproducible result in all our patients with clinically suspected meningitis. GGT is a very cost effective test and is easily available in most laboratories with less requirement of man power.

We observed that CSF GGT level was significantly elevated in pyogenic and tuberculous meningitis cases compared to controls. The rise was more in pyogenic meningitis compared to tuberculous meningitis cases. The maximum level of GGT was seen on day one (basal activity), thereafter the level declined in all the cases that survived. The cases with very high basal activity and persistent high levels were associated with poor outcome in both pyogenic and tuberculosis meningitis. This correlation was stronger in pyogenic than tuberculous group.

It was not possible to differentiate between pyogenic meningitis and tuberculous meningitis cases on the bases of CSF GGT, despite the higher level in PM group. Hence CSF GGT did not appear to have diagnostic significance.

Hence, the study is of prognostic significance as higher basal activity and persistent high level were associated with poor prognosis in both pyogenic and tuberculous meningitis.

The levels of enzyme are also correlating with other poor outcomes, other than death like raised ICP, seizures, unconsciousness and neurodeficits.

Comparing our study with those of other investigators, we found that most investigators concur with our findings.[2] However, there are a few contrarian studies found that the prognosis for individual patients cannot be established on the basis of enzymatic activity alone.[53] Another study found that determination of GGT activity in the CSF may be recommended as a supplemental method of the differential diagnosis of cerebral meningitis.[54]

The CSF GGT levels in control group were four to eight IU/L (5.6 ± 1.81 IU/L), in comparison, the cases at day one, had significantly raised GGT with a mean level of 75.05 ± 38.27 IU/L. The CSF GGT was raised to a higher level on day one, 87.82 ± 36.17 IU/L in PM and 59.44 ± 35.71 IU/L in TBM compared to day five, 31.30 ± 29.83 IU/L in PM and 22.41 ± 29.08 IU/L in TBM. There was mild to moderate GGT elevation that is up to 60 IU/L in most of the TBM cases (55%) compared to severe elevation in PM cases (77%). The CSF GGT on day one in survivor PM cases was 74.27 ± 35.79 IU/L compared to 116.6 ± 12.10 IU/L in expired PM cases showing a significant difference with a p value of 0.006 and on day five it was 17.13 ± 13.51 IU/L in survivors and 73.80 ± 24.02 IU/L in those expired with p = 0.001.

Similarly in TBM on day one, survivors had GGT level 52.40 ± 31.49 IU/L compared to expired 94.67 ± 40.81 IU/L with p = 0.05 and on day five, survivors 16.73 ± 15.50 IU/L when compared to 65.00 ± 77.7 IU/L in expired with p = 0.021.

In an Indian study authors found that, CSF GGT in control as 7.59 ± 4.61 IU/L. They studied a total of 25 cases (15 PM+ 10 TBM). In PM cases, GGT at day zero was 137 ± 35.4 IU/L, day four 112.60 ± 143.38 IU/L and day seven, 40.34 ± 66.49 IU/L and in TBM cases, GGT levels on day zero 192.46 ± 39.56 IU/L, day four, 92.15 ± 53.83 IU/L, day seven, 89.70 ± 87.33 IU/L with all significant p values. The results of this study are in concurrence with our study.[2]

Present study has thrown up a few queries most notably, the fact that GGT levels do not correlate with diagnosis. We would have expected some correlation between GGT levels and diagnosis. However this has not come to light.

There are, of course, a number of limitations in our study. Our cohort is a very small one. We had limited number of cases in some of the arms of poor out come, hence unable to show statistical significance. As the HIV positive cases were not included and TBM is more common in HIV positive patients, we do not know the impact of HIV status on CSF GGT levels.

The present study has thrown up a number of avenues for future research. If the limitations are overcome in larger studies, we would have strong guidelines for an early and efficient prognostic marker of bacterial meningitis in a resource strapped country. The test is simple and can be carried out in a central laboratory. It provides us with the information of severity of the diseases and proper triage and aggressive treatment of selected patients in a resource limited country. The test is done in serum for other indication, but not for the purpose as studied in this study. Such a prognostic marker could easily guide us in therapy in future.

CONCLUSION

The present study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on patients with meningitis and it was concluded as following;

1. The CSF GGT levels were significantly elevated in pyogenic and tuberculous meningitis cases.

2. The rise was more in pyogenic than tuberculous meningitis group.

3. The maximum GGT level was seen on Day 1, thereafter the level declined in all the cases that survived.

4. CSF GGT has prognostic significance as higher basal activity and persistent high level were associated with poor prognosis in both pyogenic and tuberculous meningitis. This correlation was stronger in pyogenic than tuberculous group.

5. CSF GGT has no diagnostic value.

SUMMARY

The present study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on patients with meningitis.

The objectives of the present study were to estimate the GGT levels in CSF serially on day one and day five of admissions in patients with pyogenic and tuberculous meningitis and to evaluate whether GGT levels have prognostic significance in cases of TBM and PM.

Present cross-sectional study was conducted on 40 patients of meningitis in the department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. Age and sex matched controls were included. The clinical profile of each patient was recorded and the necessary investigations including CSF GGT levels were done. The patients were divided into two groups, PM (22 cases) and TBM (18 cases). The CSF GGT was evaluated serially on day one and day five.

Statistically significant raise in CSF GGT was obtained on Day one and remained high on day five in both the groups with poor prognosis. CSF GGT was significantly elevated and has prognostic significance in both PM and TBM, because higher basal activity and serial rise were associated with poor programs.

BIBLIOGRAPHY

1. Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson L. Harrison's Principle of Internal Medicine. 16th Ed. New York: McGraw Hill; 2005.

2. Sharma M, Nand N. Evaluation of enzymes in pyogenic and tuberculosis meningitis. J Assoc Physicians India 2006; 54: 118-21.

3. Scheld M, Whitley RJ, Christina M. Infections of the Central Nervous System. 3rd Ed., : Lippincott Williams Wilkins; 2004

4. Parker JN, Parker PM. The Official Patient's Sourcebook on Cryptococcosis. London: Icon Group International; 2002.

5. Sakula A. Robert Koch – Founder of the science of bacteriology and discoverer of the tubercle bacillus. A study of his life and work. Br J Dis Chest 1979; 73(4): 389-94.

6. Zinsser H, Joklik WK. Zinsser Microbiology 20th Ed. Michiga: Appleton & Lange; 1992.

7. Flexner S. The results of the serum treatment in thirteen hundred cases of epidemic meningitis. J Exp Med 1913; 17: 553-76.

8. Kochar S, Marshall W. Investigations Cerebrospinal fluid. BMJ 2003; 11: 408-10.

9. Rennick G, Shann F, de Campo J. Cerebral herniation during bacterial meningitis in children. BMJ 1993; 306: 953-5.

10. Garg RK. Tuberculosis of the central nervous system. Postgrad Med J 1999; 75: 133-40.

11. Wagle NM, Vaidya AK. Diagnosis of neurotuerculosis. Indian J Pediatr 1990; 57: 657-66.

12. Chandramukhi A, Nayak P. Subacute and chronic meningitis in children – An immunological study of cerebrospinal fluid. Indian J Pediatr 1990; 57: 685-91.

13. Ungerer JPJ, Oosthuizen HM, Retief JH. Significance of adenosine deaminase activity and its isoenzymes in tuberculous effusions. Chest 1994; 106:33-7.

14. Gakis C, Calia GM, Naitana AGV, Ortu AR, Contu A. Serum and pleural adenosine deaminase activity. Correct interpretation of the findings. Chest 1991; 99: 1555-6.

15. Franco R, Valenzuela A, Lcuis C, Blanco J. Enzymatic and extraenzmatic role of ectoadenosine deaminase in lymphocytes. Immunol Rev 1998; 161: 27-42.

16. Trotta PP, Balis ME. Structural and kinetic alterations in adenosine deaminase associated with the differentiation of rat intestinal cells. Cancer Res 1977; 37: 2297-305.

17. Nyce JW. Insight into adenosine receptor function using antisense and gene knockout approaches. Trends Pharmacol Sci 1999; 20: 79-83.

18. Adair TH, Gay WJ, Montani JP. Growth regulation of the vascular system: Evidence for a metabolic hypothesis. Am J Physiol 1990; 259: R393-404.

19. Cederbaum SD, Kaitila I, Rimoin DL, Stiehm ER. The chondro-osseous dysplasia of adenosine deaminase deficiency with severe combined immunodeficiency. J Pediatr 1976; 89: 737-42.

20. Valdés L, Alvarez D, San José E, Penela P, Valle JM, García-Pazos JM, et al. Tuberculous pleuritis a study of 254 patients. Arch Intern Med 1995; 158: 2017-21.

21. Burgess LJ, Maritz FJ, Le Roux I, Taljaard JJ. Use of adenosine deaminase as a diagnostic tool for tuberculous pleurisy. Thorax 1995; 50: 672-4.

22. Koh KK, Kim EJ, Cho CH, Choi MJ, Cho SK, Kim SS, et al**.** Adenosine deaminase and carcinoembryonic antigen in pericardial effusion diagnosis, especially in suspected tuberculous pericarditis. Circulation 1994; 89: 2728-35.

23. Komsuo A, Galidela B. The diagnosic and prognostic value of adenosine deaminase in tuberculous priacarditis. Eur Heart J 1995; 16: 1126-30.

24. Binder HJ. Tuberculous peritonitis: Can ADA keep the laparoscope away? Gastroenterology 1997; 113: 687-9.

25. Voigt MD, Kalvaria I, Trey C, Berman P, Lombard C, Kirsch RE. Diagnostic value of ascites adenosine deaminase in TB peritonitis. Lancet 1989; 8: 751-4.

26. Gupta VK, Mukherjee S, Dutta SK, Mukherjee P. Diagnostic evaluation of ascitic adenosine deaminase in tubercular peritonitis. J Assoc Physicians India 1992; 40: 387-9.

27. Goldberg DM. Serum adenosine deaminase in the differential diagnosis of jaundice. BMJ 1965; 1(5431); 353-5.

28. MA Piras, C Gakis, M Budroni, G andreoni. Immunological studies in Mediterranean spotted fever. Lancet 1982;19:1249.

29. Tunas R, Siber R, Cowrylin M Gottesman. ADA activity in chronic lymphocytic leukaemia relationship to B and T cell population. J Clin Invest 1976; 57: 756-61.

30. Chawla RK, Seth RK, Raj B, Saini AS. Adenosine deaminase levels in cerebrospinal fluid in tuberculosis and bacterial meningitis. Tubercle 1991; 72: 190-2.

31. Watt G, Zaraspe G, Bautista S, Laughlin LW. Rapid diagnosis of tuberculous meningitis by suing an enzyme-linked immunosorbent assay to detect mycobacterial antigen and antibody in cerebrospinal fluid. J Infect Dis 1988; 158(10): 681-6.

32. Sada E, Ruiz-Palacios GM, lopez-vidal Y, Ponce de Leon S. Detection of mycobacterial antigens in cerebrospinal fluid of patients with tuberculous

meningitis by enzyme-linked immunosorbent assay. Lancet 1983; 2: 651-2.

33. Kalish SB, Radin RC, Levitz D, Zeiss CR, Phair JP. The enzyme-linked immunosorbent assay method for IgG antibody to purified protein derivative in cerebrospinal fluid of patints with tuberculous meningitis. Ann Intern Med 1983; 99: 630-3.

34. Hernandez R, Munoz O, Guiscafre H. Sensitive enzyme immunoassay for early diagnosis of tuberculous meningitis. Clin Microbiol 1984; 20: 533-5.

35. Abramson JS, Hampton KD, Babu S, Wasilauskas BL, Marcon MJ. The use of C-reactive protein from cerebrospinal fluid for differentiating meningitis form other central nervous system diseases. J Infect Dis 1985; 15(5): 854-8.

36. Corral CJ, Pepple JM, Moxon ER, Hughes WT. C-reactive protein in spinal fluid of children with meningitis. J Pediatr 1981; 99: 365-9.

37. Rattan A. Diagnosis of tuberculosis by polymerase chain reaction. Indian J Pediatr 1990; 57: 673-7.

38. Jinkins JR, Gupta R, Chang KH, Rodriguez-Carbhajal J. MR imaging of central nervous system tuberculosis. Radiol Clin North Am 1995; 33(4): 771-86.

39. de Castro CC, de Barros NG, Campos ZM, Cerri GG. CT scans of cranial tuberculosis. Radiol Clin North Am 1995; 33(4): 753-69.

40. Mardh PA, Larson L, Hoiby N. Tuberculostearic acid as a diagnostic marker in tuberculous meningitis. Lancet 1983; 1: 367.

41. Taylor LM, Smith HV, Hunter G. The blood-CSF barrier to bromide in diagnosis of tuberculous meningitis. Lancet 1954; 1: 700-2.

42. Din MU, Diju IU, Tabassum R, Hussain ST. Free sialic acid in CSF in the differential diagnosis of meningitis. Indian J Med Res 1981; 74: 604-6.

43. Smith SM, Eng RH, Campos JM, Chmel H. D-lactic acid measurements in the diagnosis of bacterial infections. J Clin Microbiol 1989; 27: 385-460.

44. Prasad R, Kumar A, Khanna BK, Mukeriji PK, Agarwal SK, Umar A, et al. Adenosine deaminase activity in cerebro-spinal fluid for diagnosis of tubercuous meningitis. Ind J Tub 1991; 38: 99-102.

45. Daniel TM, Debanne SM. The serodiagnosis of tuberculosis and other myocobacterial disease by ELISA. A Rev Respir Dis 1987; 135: 1137-51.

46. Bishop ML, Duben-Engelkirk JL, Fody EP. Clinical chemistry: Principles, procedures, correlations. 4th Ed. Philadelphia: Lippincott Williams and Wilkins; 2000.

47. Murry RK, Granner DK, Mayes P, Rodwell VW. Harper's illustrated biochemistry. 26th Ed., Boston: McGraw Hill Company; 2003.

48. Schiff ER, Sorell MF, Maddrey WC. Schiffs diseases of the Liver. 8th Ed. Washington: Lippincott Raven Publishers; 1999.

49. Delvin TM. Textbook of biochemistry with clinical correlations. 4^{th} Ed., New York: Wiley-Liss Publishers; 1997.

50. Berg JM, Tymoczko JL, Stryer L. Biochemistry. 5^{th} Ed., New York: W. H. Freeman and Company; 2002.

51. Burtis CA, Ashwood ER, Bruns DE. Tietz textbook of clinical chemistry and molecular diagnostics. 4^{th} Ed., New Delhi: Elsevier India Pvt. Ltd.; 2006.

52. Kaplan A, Jack R, Opheim KE, Toivola B, Lyon AW. Clinical chemistry, interpretation and techniques. 4^{th} Ed., Malvern: Williams and Wilkins; 1995.

53. Lutsar I, Haldre S, Topman M, Talvik T. Enzymatic changes in cerebrospinal fluid in patients with infections of the central nervous system. Acta Paediatr 1994; 83 (11): 1146 -50.

54. Akimov GA, Komandenko NI, Zinchenko VA. Activity of gamma glutamyl transferase in the cerebrospinal fluid in various forms of cerebral arachnoiditis. Zh Neropatol Psikhiatr Im SS Korsakova 1986; 86(5): 682-4.

55. Radzivil GG, Roslyi IM. Enzymologic diagnosis of cerebral lesions in generalised forms of meningococcal infection in the acute period. Zh Nevropatol Psikhiatr Im SS Korsakova 1989; 89 (2): 10 – 5.

56. Solberg HE, Theodorsen L, Stromme JH. Gamma glutamyl transferase in human serum analysis of kinetic models. American Assoc Clinical Chemistry 1981; 27: 303-307.

57. Shaw LM, Stromme JH, London JL, Theodorsen L. IFCC methods for the determination of enzyme part 4, IFCC method for gamma-glutamyl transferase [(gamma-glutamyl)-peptide; amino acid gamma-glutamyl transferase, EC 2.3-2.2]. Clinica Chemia Acta 1983; 15F – 338F.

58. Takayanagi M, Yamamoto K, Nakagawa H, Iinuma K. Factors associated with the prognosis of bacterial meningitis. No To Hattatsu 1997; 29(4): 291-7.

ANNEXURE I – CONSENT FORM

Objective and Purpose of the study

This is a study of prognostic efficacy of gamma glutamyl transpeptidase in cerebrospinal fluid in pyogenic and tuberculous meningitis. The principal investigator of the study is Dr. Srinivas B. and the co-investigator is Dr. Nitinkumar Agarwal. This research is intended to study the prognostic efficacy of gamma glutamyl transpeptidase in cerebrospinal fluid in pyogenic and tuberculous meningitis and my co-operation will be of great help to the patients of pyogenic and tuberculous meningitis in future.

Procedure

If I agree to be a part of the study I will be asked the relevant history and will be subjected to relevant clinical examination and biochemical investigations like CSF study, CSF will be collected by lumbar puncture using 20 or 22 G spinal needle on day one and day five and some blood investigation.

Risk and Benefit

The only risk and possible discomfort I might get while taking blood from my arm, it may cause swelling, pain, redness, bruising or infection (rarely happens) at the site where needle is inserted and headache following lumbar puncture.

Alternatives

Taking part in this study is voluntary. I may choose not to take part in this study, or if I decide to take part I can later change my mind and withdraw from the study. My decision will not change the present or future health care or other services that I receive. The study doctor or sponsor may stop my participation in this study any time. If I choose not to take part in the study I will receive standard treatment for patients with my condition.

Privacy and Confidentiality

All information collected about me during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify me in this research record.

Institutional / Sponsors Policy

Does not apply to this research.

Financial Incentives for Participation

I will not be charged any amount for the investigations subjected to me. I will not receive compensation or reimbursement for taking part in this study.

Authorization to Publish Results

Information from this study may be published but my identity will be confidential in any publication.

Consent Statement

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, this entire consent form, and have had all my questions answered.

Name of Study Participant or legally authorised representative:

Signature / Thumb Print

In case of the queries during study or in future I may contact following person

Principal investigator	: Dr. Srinivas B.	Phone	: 0831-2473787
Co-Investigator	: Dr. Nitinkumar Agarwal	Phone	: 94481 03015

Name of Witness	:	Signature	:
Investigator Name	:	Signature	:
Date	:	Place	:

ANNEXURE II – PROFORMA

I. Patient Identification

Name	:	Age / Sex	:	I.P. No:
Address	:	DOA	:	
DOD/DOE	:	Outcome	: Improved / Expired	
Occupation	:	Religion	:	

II. History

a. Fever

Duration :

Type : Continuous/Intermittent /Remittent

Associated Symptoms : Chills / Rigors / Sweating

b. Headache

Onset : Sudden / Insidious

Duration :

Site : Generalised / Localised

Character : Dull Aching / Throbbing

Associated Symptoms : Neck Pain / Stiffness

c. Vomiting

Duration :

Nature : Projectile / Spontaneous / induced

Frequency :

Associated symptoms : Nausea

d. Mental Changes

Consciousness	:	Irritable / Drowsy / Stuperous / Comatose / Delirious
e. Convulsions	:	Yes / No If Yes, Details __________
f. Neurological Deficits	:	Yes / No If Yes, Details __________
g. Visual disturbances	:	Photophobia/Diplopia/Blurring of vision
h. Other symptoms	:	Details ________________________

i. Symptoms relating to other system involvement

Lungs	:	Cough with expectoration / Chest pain / breathlessness / Hemoptysis
Ear	:	Discharge / Deafness
Liver	:	Icterus / Ascites
Any other	:	

III. Past History

TB / HIV status / Diabetes / Jaundice / Symptoms relating to other system involvement.

IV. Personal History

Diet	:	Bowel	:
Appetite	:	Bladder	:
Sleep	:	Habits	: Alcoholism

V. General Physical Examination

Pallor	:
Icterus	:
Lymph nodes	:
Temperature	:
Pulse	:
Blood pressure	:
Respiratory rate	:

VI. CNS

Mental functions	:	Level of consciousness
Speech	:	
Orientation to Time / Place / Person	:	
Memory	:	Recent / Past
Emotional status and behaviour	:	
Hallucination and Delusion	:	
Fundus	:	
Cranial Nerves	:	
Motor System	:	
Reflexes	:	
Deep tendon reflexes	:	
Plantars	:	
Abdominal	:	
Cremastric	:	
Corneal	:	

Organic reflexes

Deglutition :

Bowel :

Bladder :

Sensory System :

Co-ordination :

Signs of meningeal irritation :

Neck rigidity :

Kernig's Sign :

Brudzinski's : Neck sign

Leg sign

Skull and spine :

VII. Other Systems

Respiratory system :

Cardiovascular system :

Per abdomen :

Others :

VIII. Investigations

Haemoglobin% :

Total leukocyte count :

Differential count :

ESR :

Liver function test :

Random blood sugar :

Chest X-ray	:	
CSF	:	
Appearance	:	Clear / turbid / opalescent / purulent / xanthochromic
Cell count	:	
Cell type	:	
Protein	:	
Sugar	:	
Gram's Stain	:	
Z-N stain for AFB	:	
Culture	:	
ADA	:	
India Ink	:	
GGT	:	Day 1 Day 5
Neuroimaging	:	

IX. Symptoms and signs related investigation

FNAC of lymph node :

Culture / sensitivity /Z-N
staining of discharging focus :

X. Final Diagnosis

ANNEXURE III – PHOTOGRAPHS

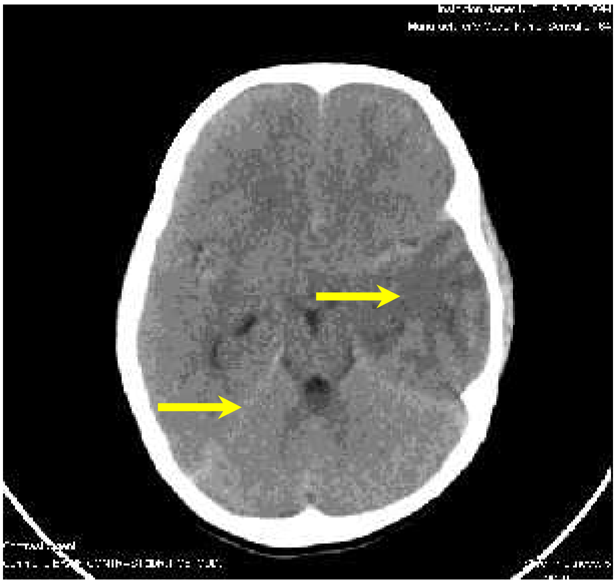


Figure No. 1: CT scan of brain showing cerebral edema with meningeal enhancement

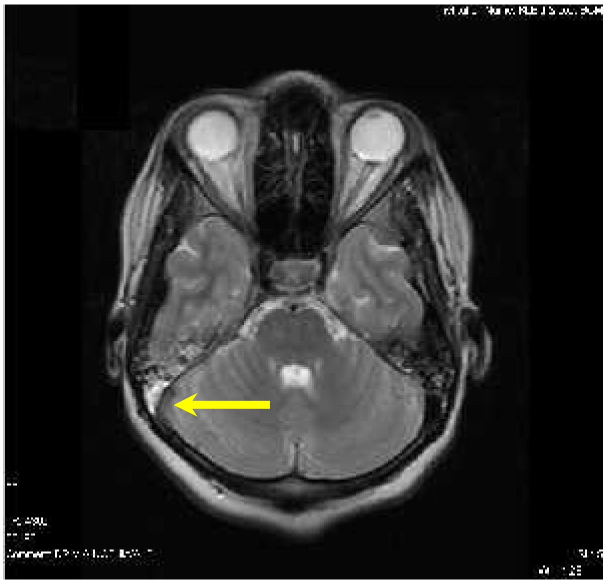


Figure No. 2: MRI of Brain showing right side mastoiditis with chronic suppurative otitis media with right sigmoid and transverse sinus thrombosis

MASTER CHART

Sr. No.	IP No.	Group	Age (Yrs)	Sex	Fever (Days)	Headache (Days)	Vomiting (Days)	Alt Sen		Convulsions (Episodes)	Vis Dist		Neck Stiffness	Kernig's	Brudzinski's neck	Brudzinski's Leg	Neurodeficits	Fundus	TLC (/mm^3)	ESR (mm @1 hour)	CXR	Cerebrospinal Fluid											Neuroimaging	Others	Final diagnosis	Outcome
								Level	Duration (Days)		Disturbance	Duration (Days)										Cell count (mm^3)	Lymphocyte (%)	Neutrophils (%)	Protein (mg%)	Sugar (mg%)	Gram's stain	Smear (AFB)	Bacterial Culture	ADA (U/L)	GGT (IU/L) Day 1	GGT (IU/L) Day 5				
1	208008	CA	15	M	3	3	2	DR	1	-	PH	3	+	+	-	-	-	N	8,400	48	N	92	90	10	80	40	-	-	-	30	46	2	CT N	-	TB MEN	I
2	209026	CA	16	F	2	4	1	-	-	-	PH	2	+	-	-	-	L VII CN	N	14,400	20	N	220	20	80	200	20	GPC	-	SPY	8	102	22	CT N	L ED SPY	A O PY MEN	I
3	210042	CA	16	M	5	4	4	IR	2	-	PH	4	+	-	-	-	-	N	18,000	20	N	200	15	85	140	16	-	-	SPN	4	80	40	CT N	-	A PY MEN	I
4	220186	CA	76	M	3	-	-	ST	2	-	-	-	+	+	-	-	-	BlP	18,900	26	R LZP	360	10	90	190	70	GPC	-	SPN	6	110	87	CT CE	SP SPN	A PY MEN, L LB PNEU T-II DM	E
5	222426	CA	26	F	5	5	-	-	-	-	-	-	+	-	-	-	-	N	7,800	42	N	40	80	20	90	32	-	-	-	36	56	20	CT N	LN TB	TB MEN, TB CE LYMPH	I
6	224210	CA	26	F	-	5	1	IR	1	-	PH	3	+	-	-	-	-	N	9,200	50	R UZK	90	90	10	140	32	-	-	-	40	70	50	CT N	SP AFB	TB MEN, PULM TB	I
7	226042	CA	36	M	4	3	2	-	-	-	PH	2	+	-	-	-	-	N	10,200	36	N	80	90	10	100	30	-	-	-	42	86	20	CT N	-	TB MEN	I
8	226220	CA	35	F	5	5	2	IR	2	-	PH	1	+	+	-	-	-	N	20,100	20	N	180	10	90	120	10	GNC	-	KP	10	70	10	CT N	UR KP	A PY MEN, UTI	I
9	228216	CA	78	M	2	-	-	ST	1	-	PH	2	-	-	-	-	-	BlP	21,400	16	L AP	310	10	90	86	40	GPC	-	SPN	8	96	36	CT CE	-	A PY MEN, ASP PNEU	E
10	231136	CA	56	F	5	4	-	IR	1	-	BL	1	+	+	-	-	Bl VI CN	EP	7,900	30	N	40	90	10	80	40	-	-	MTB	40	102	40	CT LI	-	TB MEN	I
11	236349	CA	60	F	3	5	-	IR	2	-	BL,DI	3	+	+	-	-	L VI CN	EP	22,000	20	N	220	10	90	100	20	-	-	SPN	10	80	5	CT FS	-	A PY MEN, REC SIN	I
12	237210	CA	22	M	-	3	-	IR	2	-	BL	1	+	-	-	-	-	BlP	10,200	32	N	80	86	14	68	30	-	-	-	26	76	10	CT N	-	TB MEN	I
13	238856	CA	58	M	3	3	3	ST	1	2	-	-	+	+	-	-	L HPL	BlP	26,400	18	R AP	240	12	88	102	10	GPC	-	SPN	8	120	100	MRI CE LI	-	A PY MEN, T-II DM	E
14	240286	CA	32	M	4	2	1	DR	1	-	PH,DI	2	+	-	-	-	Bl VI CN	N	18,200	18	N	250	10	90	120	30	-	-	EC	8	80	25	CT CE	UR EC	A PY MEN, UTI	I
15	241024	CA	62	F	2	5	1	-	-	-	PH,DI	2	+	-	-	-	-	N	16,100	20	N	56	20	80	82	40	-	-	SPN	2	8	2	CT FS	-	A PY MEN, CHR SIN	I
16	242120	CA	15	M	4	5	2	-	-	-	-	-	+	-	-	-	-	N	6,800	80	R UZK	48	80	20	1020	30	-	-	-	26	4	2	CT N	SP AFB	TB MEN, PULM TB	I
17	243214	CA	15	M	5	5	5	ST	3	2	-	-	+	+	-	-	-	BlP	21,000	10	Bl AP	220	10	90	108	10	GPC	-	SPY	-	130	-	CT CE	-	A PY MEN, ASP PNEU	E
18	244826	CA	28	F	3	3	1	IR	1	-	-	-	+	-	-	-	-	N	7,200	82	N	36	90	10	101	30	-	-	-	28	50	10	CT N	-	TB MEN	E
19	245216	CA	28	M	5	5	2	-	-	-	-	-	+	-	-	-	-	N	8,600	76	N	32	90	10	86	32	-	-	-	30	20	5	CT N	-	TB MEN	I
20	246420	CA	28	M	4	3	-	-	-	-	PH	2	+	-	-	-	-	N	18,000	18	N	186	5	95	70	28	-	-	SPN	-	40	2	CT FS	-	A PY MEN, CHR SIN	I
21	247210	CA	70	M	4	4	2	DR	1	-	BL	2	+	-	-	-	-	EP	22,100	20	L UZP	350	5	95	180	80	-	-	KP	10	134	44	MRI N	SP KP, BC KP	A PY MEN, L LB PNEU T-II DM	I
22	249228	CA	18	F	5	5	-	-	-	-	-	-	+	-	-	-	-	N	6,500	76	L UZK	90	100	0	100	32	-	-	-	20	36	10	MRI N	-	TB MEN, PULM TB	I
23	249556	CA	25	F	3	2	-	ST	1	-	BL	2	+	+	-	-	-	BlP	14,100	78	BL EBK	258	90	10	205	40	-	-	-	36	130	-	CT CE, BE, NCH	-	TB MEN, ENDO BR TB	E
24	250201	CA	15	F	3	3	-	-	-	-	DI	2	+	+	-	-	Bl VI CN	BlP	18,300	18	N	150	8	92	76	14	-	-	SPN	-	62	5	CT R Ma	R ED SPN	A O PY MEN	I

MASTER CHART

Sr. No.	IP No.	Group	Age (Yrs)	Sex	Fever (Days)	Headache (Days)	Vomiting (Days)	Alt Sen		Convulsions (Episodes)	Vis Dist		Neck Stiffness	Kernig's	Brudzinski's neck	Brudzinski's Leg	Neurodeficits	Fundus	TLC (/mm^3)	ESR (mm @1 hour)	CXR	Cell count (mm^3)	Lymphocyte (%)	Neutrophils (%)	Protein (mg%)	Sugar (mg%)	Gram's stain	Smear (AFB)	Bacterial Culture	ADA (U/L)	GGT (IU/L)		Neuroimaging	Others	Final diagnosis	Outcome
								Level	Duration (Days)		Disturbance	Duration (Days)																			Day 1	Day 5				
25	250926	CA	26	F	4	5	2	IR	2	-	PH	2	+	-	-	-	-	N	17,800	10	N	100	10	90	110	20	GPC	-	SAU	10	56	20	CT N	USG ASC	A PY MEN, PP BACT, NUTR ANAE	I

MASTER CHART

								Alt Sen			Vis Dist											Cerebrospinal Fluid									GGT (IU/L)				
Sr. No.	IP No.	Group	Age (Yrs)	Sex	Fever (Days)	Headache (Days)	Vomiting (Days)	Level	Duration (Days)	Convulsions (Episodes)	Disturbance	Duration (Days)	Neck Stiffness	Kernig's	Brudzinski's neck	Brudzinski's Leg	Neurodeficits	Fundus	TLC (/mm^3)	ESR (mm @1 hour)	CXR	Cell count (mm^3)	Lymphocyte (%)	Neutrophils (%)	Protein (mg%)	Sugar (mg%)	Gram's stain	Smear (AFB)	Bacterial Culture	ADA (U/L)	Day 1	Day 5	Neuroimaging	Others	Final diagnosis
26	251086	CA	16	M	4	3	-	ST	1	-	-	-	+	+	+	-	-	BlP	18,600	16	N	160	5	95	100	22	GNB	-	NM	-	126	-	CT CE	-	A PY MEN
27	251126	CA	46	M	3	3	1	IR	1	1	DI,BL	2	+	+	-	-	Bl VI CN	BlP	12,000	60	N	250	95	5	200	26	-	-	-	36	104	120	CT CE, BE	-	TB MEN, PR HTN
28	252121	CA	68	F	4	4	-	IR	1	-	-	-	+	-	-	-	-	HTR	13,300	16	N	80	10	90	96	30	-	-	LM	4	26	2	CT N	-	A PY MEN
29	252226	CA	40	M	4	5	-	-	-	-	-	-	+	-	-	-	-	N	9,800	48	N	52	90	10	120	36	-	-	-	40	20	2	CT N	-	TB MEN
30	252312	CA	65	M	3	3	2	DR	1	-	-	-	+	-	-	-	R HPL	BlP	16,700	12	N	256	6	94	160	26	-	-	SPY	6	126	76	CT L ICI, CE	BC SPN	A PY MEN, R HPL
31	252346	CA	28	F	5	5	-	IR	1	-	BL	1	+	+	-	-	Bl VI CN	BlP	10,200	76	MM	80	90	10	102	30	-	-	-	26	32	10	CT N	BAL AFB	MIL TB, TB MEN
32	253042	CA	36	M	-	1	1	ST	1	2	-	-	+	+	+	-	-	BlP	15,600	12	N	146	10	90	132	12	-	-	KP	-	78	24	MRI CVT	-	A PY MEN, CVT
33	253542	CA	26	M	2	2	-	IR	1	1	-	-	+	-	-	-	Bl VI CN, R HPL	BlP	14,200	10	N	180	10	90	102	18	-	-	SPN	-	140	26	CT CVT, VI	-	A PY MEN, CVT, L ER ASOM
34	253923	CA	18	F	4	5	1	-	-	-	-	-	+	-	-	-	-	N	7,800	42	R UZK	40	100	0	100	40	-	-	-	24	10	2	CT N	SP AFB	TB MEN, PULM TB
35	257744	CA	32	F	-	3	2	IR	1	-	-	-	+	-	-	-	-	N	16,200	18	N	350	10	90	100	18	GPC	-	SPN	10	98	20	CT N	-	A PY MEN
36	271303	CA	35	M	-	5	-	-	-	-	-	-	+	-	-	-	-	EP	14,000	78	N	120	70	30	140	34	-	-	-	26	60	18	CT CE	-	TB MEN
37	276621	CA	30	F	5	5	-	IR	2	-	DI	3	+	-	-	-	L HPL	EP	9,800	40	N	250	80	20	300	40	-	-	-	20	98	40	MRI R ICI	-	TB MEN, L HPL
38	278466	CA	22	F	5	5	4	ST	1	-	DI	2	+	+	+	+	R HPL, L III,IX,X, L HC	N	11,000	36	N	80	90	10	90	40	-	-	-	28	70	20	MRI R BGI, L FLI	ECHO RHD MS	TB MEN, VAS, R HPL, MCNP, HC, RHD
39	278480	CA	50	F	3	3	3	DR	2	-	-	-	+	+	-	-	-	BlP	22,000	18	Bl AP	1000	16	84	600	20	GPC	-	-	8	110	70	CT CE	-	A PY MEN, ASP PNEU, T-II DM
40	279334	CA	15	M	5	5	2	IR	1	-	-	-	+	+	-	-	Bl VI CN	EP	16,000	20	N	120	12	88	100	30	-	-	KP	6	60	10	CT N	-	A PY MEN
41	209293	CL	70	M	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6	-	-	-	R DIR ING HERN OP, ↓SA
42	212022	CL	26	F	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6	-	-	-	FTP, LSCS, ↓SA
43	212204	CL	22	M	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	-	-	-	HYD-JOUB PROC, ↓SA
44	220628	CL	26	F	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	8	-	-	-	A APPEND, OP APPENDE, ↓SA
45	235018	CL	36	M	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	L DIR ING HERN OP, ↓SA
46	232625	CL	52	M	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	8	-	-	-	HYD-JOUB PROC, ↓SA
47	242120	CL	25	M	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6	-	-	-	HYD-JOUB PROC, ↓SA
48	253021	CL	32	M	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6	-	-	-	FIS ANO LAT SPHINCT, ↓SA
49	272003	CL	50	M	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	-	-	-	HYD-JOUB PROC, ↓SA

MASTER CHART

Sr. No.	IP No.	Group	Age (Yrs)	Sex	Fever (Days)	Headache (Days)	Vomiting (Days)	Alt Sen		Convulsions (Episodes)	Vis Dist		Neck Stiffness	Kernig's	Brudzinski's neck	Brudzinski's Leg	Neurodeficits	Fundus	TLC (/mm^3)	ESR (mm @1 hour)	CXR	Cell count (mm^3)	Lymphocyte (%)	Neutrophils (%)	Protein (mg%)	Sugar (mg%)	Gram's stain	Smear (AFB)	Bacterial Culture	ADA (U/L)	GGT (IU/L)		Neuroimaging	Others	Final diagnosis
								Level	Duration (Days)		Disturbance	Duration (Days)																			Day 1	Day 5			
50	280181	CL	38	F	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6	-	-	-	AC APPEND, OP APPENDE, ↓SA

MASTER CHART

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MASTER CHART

Outcome
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ANNEXURE IV – KEY TO MASTER CHART

+	-	Present
-	-	Absent
@	-	At
A	-	Acute
ADA	-	Adenosine deaminase
AFB	-	Acid fast bacclli
Alt Sen	-	Altered sensorium
ANAE	-	Anaemia
AP	-	Aspiration Pneumonia
APPEND	-	Appendicitis
APPENDE	-	Appendicectomy
ASC	-	Ascites
ASOM	-	Acute suppurative otitis Meida
ASP	-	Aspiration
BACT	-	Bacteremia
BAL	-	Broncho alveolar lavage
BC	-	Blood culture
BE	-	Basal Exudates
BGI	-	Basal ganglia infarct
BL	-	Blurring
Bl	-	Bilateral
BlP	-	Bilateral Papilledema
CA	-	Cases

CE	-	Cerebral Edema
CE LYMPH	-	Cervical lymphadenopathy
CHR	-	Chronic
CL	-	Control
CN	-	Cranial Nerve
CT	-	Computed tomography
CVT	-	Cortical venous thrombosis
CXR	-	Chest x-ray
DI	-	Diplopia
DIR	-	Direct
DR	-	Drowsy
E	-	Expired
EBK	-	Endobronchial Koch's
EC	-	Escherichia Coli
ECHO	-	Echocardiogram
ED	-	Ear discharge
ENDO BR	-	Endobronchial
EP	-	Early papilledema
ER	-	Ear
ESR	-	Erythrocyte Sedimentation Rate
F	-	Female
FIS	-	Fissure
FLI	-	Frontal lobe infarct
FS	-	Frontal Sinusitis
FTP	-	Full term pregnancy

GGT	-	Gamma Gutamyl Transpeptidase
GNB	-	Gram negative Bacilli
GNC	-	Gram Negative cocci
GPC	-	Gram Positive cocci
HC	-	Hemichorea
HERN	-	Hernia
HPL	-	Hemiplegia
HTN	-	Hypertension
HTR	-	Hypertensive retinopathy
HYD	-	Hydrocoele-
I	-	Improved
ICI	-	Internal Capsule infarct
ING	-	Ingunial
IP. No.	-	In Patient Number
IR	-	Irritable
JOUB	-	Joubley's
KP	-	Klebsiella pneumoniae
L	-	Left
LAT	-	Lateral
LB	-	Lobe
LI	-	Lacunar infarct
LM	-	Listeria monocytogenes
LN	-	Lymph Node
LSCS	-	Lower Segment Caesarean Section
LZP	-	Lower zone pneumonia

M	-	Male
Ma	-	Mastoiditis
MCNP	-	Mulitple Cranial nerve Palsies
MEN	-	Meningitis
MIL	-	Miliary
MM	-	Miliary Mottling
MRI	-	Magnetic Resonance Imaging
MS	-	Mitral Stenosis
MTB	-	Mycobacterium tuberculosis
mg%	-	mili gram percent
mm^3	-	cubic milli meter
N	-	Normal
NCH	-	Non-communicating hydrocephalus
NM	-	Nisseria Meningitidis
NUTR	-	Nutritional
O	-	Otogenic
OP	-	Operated
PH	-	Photophobia
PNEU	-	Pneumonia
PM	-	Pyogenic Meningitis
PP	-	Postpartum
PR	-	Primary
PROC	-	Procedure
PULM	-	Pulmonary
PY	-	Pyogenic

R	-	Right
REC	-	Recurrent
RHD	-	Rheumatic Heart Disease
RS	-	Remained Same
SA	-	Spinal Anaesthesia
SAU	-	Straphylococcus Aureus
SIN	-	Sinusitis
SP	-	Sputum
SPHINCT	-	Sphincterotomy
SPN	-	Streptococcus pneumoniae
SPY	-	Streptococcus pyogenus
Sr. No.	-	Serial Number
ST	-	Stuperous
T II DM	-	Type 2 Diabetes Mellitus
TB	-	Tuberculosis
TLC	-	Total leucocyte count
USG	-	Ultra Sonography
UR	-	Urine
UTI	-	Urinary tract infection
UZK	-	Upper zone Koch’s
UZP	-	Upper zone Pneumonia
VAS	-	Vasulitis
VI	-	Venous infarct
Vis Dis	-	Visual Disturbance
Yrs	-	Years