"A STUDY ON ESTIMATION OF CORTISOL LEVELS IN CEREBROSPINAL FLUID FOR DIFFERENTIATING BACTERIAL FROM NON BACTERIAL MENINGITIS"

Dissertation Submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY

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with partial fulfilment of the regulations

for the award of the degree of

M.D. GENERAL MEDICINE

COIMBATORE MEDICAL COLLEGE,

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CERTIFICATE

Certified that this is the bonafide dissertation done by **Dr. Manjunath.B.V** and submitted in partial fulfillment of the requirements for the Degree of **M.D General Medicine**, Branch I of **The Tamilnadu DR. M.G.R. Medical University Chennai.**

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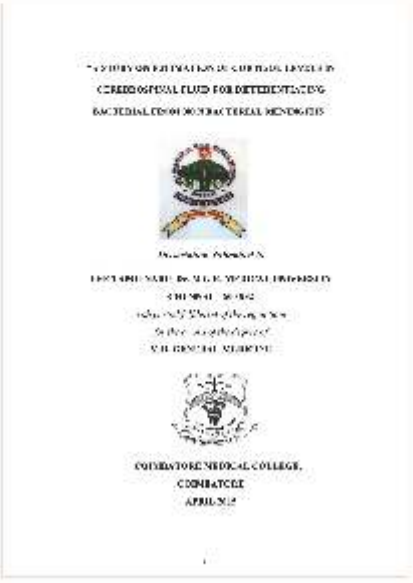

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DECLARATION

I solemnly declare that the dissertation titled **"A study on estimation of Cortisol levels in Cerebrospinal fluid for differentiating Bacterial from Non-Bacterial meningitis "** was done by me from August 2013 to July 2014 under the guidance and supervision of Professor **Dr.KUMAR NATARAJAN .M.D.**

This dissertation is submitted to the Tamilnadu Dr. M.G.R. Medical University towards the partial fulfillment of the requirement for the award of MD Degree in General Medicine (Branch I).

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DATE: **Dr. Manjunath.B.V**

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ABSTRACT

Purpose of the Project:

Meningitis remains serious clinical problem in developing countries.Delayed diagnosis and treatment remit in significant morbidity and mortality. Meningitis represents a serious disease that is associated with significant morbidity and mortality. Outcomes of bacterial meningitis have remained stable since the advent of antibiotics, with the case fatality being as high as 25%. Long-term sequelae such as hearing loss, palsies and personality changes affect approximately 40% of survivors. Early antibiotic therapy is crucial for optimizing the outcome of bacterial meningitis. Therefore, it is important to distinguish bacterial meningitis from aseptic meningitis during the acute phase of the disease, when clinical symptoms are often similar as this could help to avoid complications and to limit unnecessary antibiotic use .However, a sensitive laboratory test that is easy to perform is still required, so that all patients with bacterial meningitis can be identified reliably on admission.

Background:

Signs and symptoms, results of routineCSF analysis and radiological findings are inadequate in making a definitive diagnosis. Gram's stain and AFB stain of CSF are rapid technique for detection of organism but lack sensitivity.Similarly CSF culture is another method of

diagnosis but it is time consuming.PCR is highly specific and sensitive but costly and not widely available. In the view of these limitations, determination of CSF CORTISOL levels in differentiating bacterial from nonbacterial meningitis is useful as a diagnostic and valuable marker.

Aims and Objectives:

The study was aimed to evaluate the utility of CSF Cortisol in differentiating Bacterial from Non Bacterial meningitis.

Data Collection and the Source:

For all patients admitted in CMCH, who fulfilled the inclusion and exclusion criteria CSF cortisol estimation is done and routine CSF analysis for diagnosing meningitis. 10 normal control subjects with no neurological illness undergoing spinal anesthesia are included. Control CSF cortisol estimation is done. Informed consent was taken from all patients.

Methods:

A cross sectional observational study was done in forty of suspected meningitis of varied etiologies and 10 control subjects without any pre-existing neurological disorders who have undergone lumbar punctureduring spinal anesthesia were included in the study. All the patients were thoroughly examined clinically by preformed proforma and investigated.

Case definition:

Patients with clinical suspicion of meningitis presenting with fever, vomiting, altered sensorium, and nuchal rigidity.

Results:

Mean cerebrospinal fluid cortisol activity was 13.06µg/dl,4.44µg/dl, 2.29µg/dl and 1.05µg/dl in neutrophilic meningitis, lymphocytic meningitis, aseptic meningitis and controls respectively. Mean CSF-Cortisol level in neutrophilic meningitis was significantly higher as compared to other groups.

Conclusion:

CORTISOL activity in CSF is a rapid, relatively inexpensive and simple procedure, and can be of great value in the early differentiation of neutrophilic, lymphocytic and aseptic meningitis, thus helping in earlier institution of appropriate treatment and thereby decreasing morality and complications.

Key words: CSF-Cerebrospinal fluid, Cortisol, Neutrophilic meningitis, lymphocytic meningitis and aseptic meningitis.

INTRODUCTION

Meningitis is defined as inflammation of the leptomeninges and underlying subarachnoid cerebrospinal fluid (CSF). Meningitis is the inflammation of the protective membranes covering the central nervous system, known collectively as the meninges[1].

Meningitis is a turning out to be major problem of the world. Meningitis is the result of various etiologies factors can be categorized into pyogenic, tubercular or aseptic meningitis.

Of these, bacterial meningitis is a common infectious disease of the CNS in developing countries like India, and also a major global health problem even in the developed countries of the world. It represents a serious disease associated with significant morbidity and mortality[2]. Furthermore, long-term sequelae such as hearing loss, cranial nerve palsies and personally changes affect approximately 40% of survivors[3].

Pneumococcal, Haemophilus influenza and meningococcal meningitis have a worldwide distribution, mainly seen m young age groups. Since the introduction of vaccine against these agents, incidence of meningitis has dramatically reduced in developed countries. But incidence remains the same in the developing world.

Signs and symptoms, results of routine CSF analysis and radiological fading are often inadequate m ticking a definitive diagnosis.

Clearly a prompt laboratory test is required to differentiate these various types of meningitis Gram's stain and AFB stain of CSF are rapid methods of detection of organism, but lack sensitivity.

Similarly, culture of CSF is another method of diagnosis but it is time consuming.

PCR test is a highly sensitive and specific test but is very coaly and not widely available.

Therefore, for differentiation among various types of meningitis, a reliable and cost effective test should be available.

In view of all these limitations, determination of CSF-CORTISOL activity may be a diagnostic and valuable marker in differentiating bacterial from nonbacterial meningitis[4].

Detection of high level of CSF cortisol has shown promising results in the diagnosis Bacterial meningitis.

The main purpose of this study is to evaluate utility of CSF CORTISOL in differentiating bacterial from nonbacterial meningitis.

Aims of the Study

1. To evaluate the utility of CSF Cortisol levels in differentiating Bacterial and Non-Bacterial meningitis.

2. To study CSF Cortisol levels in Bacterial (neutrophilic) and Non-Bacterial (lymphocytic and aseptic) meningitis.

REVIEW OF LITERATURE

Review of history:

CSF was discovered by DomenicoLentango in 1774 and Carnig was the first to puncture the subarachnoid space in living person.

Pepavoine described in 1830 the anatomical nature of tuberculous meningitis and called it as “ArachnoiditisTuberculosa''.

Gren PH coined the term tuberculous meningitis in 1836.

Robert Koch discovered the acid fast bacilli on 24th March 1882.

Valdmer Kernig described the Kernig’s sign in 1884.

HenrichQuincke in 1891 devised plain needle for lumbar puncture, thus greatly facilitating the study of CSF for diagnostic purposes.

Brudzinski in 1909 described neck sign consisting of passive flexion of neck resulting in flexion of knee and hips. The Brudzinski's sign is more sensitive if neck flexion is attempted with patient in a sitting position with legs extended parallel to the floor. In his original paper he also described leg sign.

Mastertzed in 1912 reported the chemical composition of CSF in meningitis.

In 2006, Sunit C Singhi et al suggested Serum cortisol could be useful in assessment of acute bacterial meningitis[5]. Similarly, CSF cortisol was adopted for diagnosis of bacterial meningitis.

Anatomy and Physiology

The human brain and spinal cord is covered by protective coverings called meninges. They are three in number and are named as the pia mater (the inner most), the arachnoid mater (the intermediate layer), and the Dura mater (the outer most layers).

Dura mater

It is also called as pachymenix. The two layers of cranial Dura are outer endosteal (periosteal layer) layer and inner meningeal layer.

The periosteal layer of Dura is covering the internal surface of the cranial bones. This Dural layer is continuous with the periosteum of the cranium around the foramina margins.

The meningeal layer (Dura mater proper) is a dense and strong membrane around the brain. The dura proper continuous below as dural covering of the spinal cord. This layer forms sheaths for the exiting cranial nerves passing through the skull foramina.

The meningeal layer has four septa inside skull that divide the cranial cavity into multiple spaces that communicate freely. The function of these septa is to prevent the brain displacement due to acceleration and deceleration forces, during head movement.

Reflections of dura:

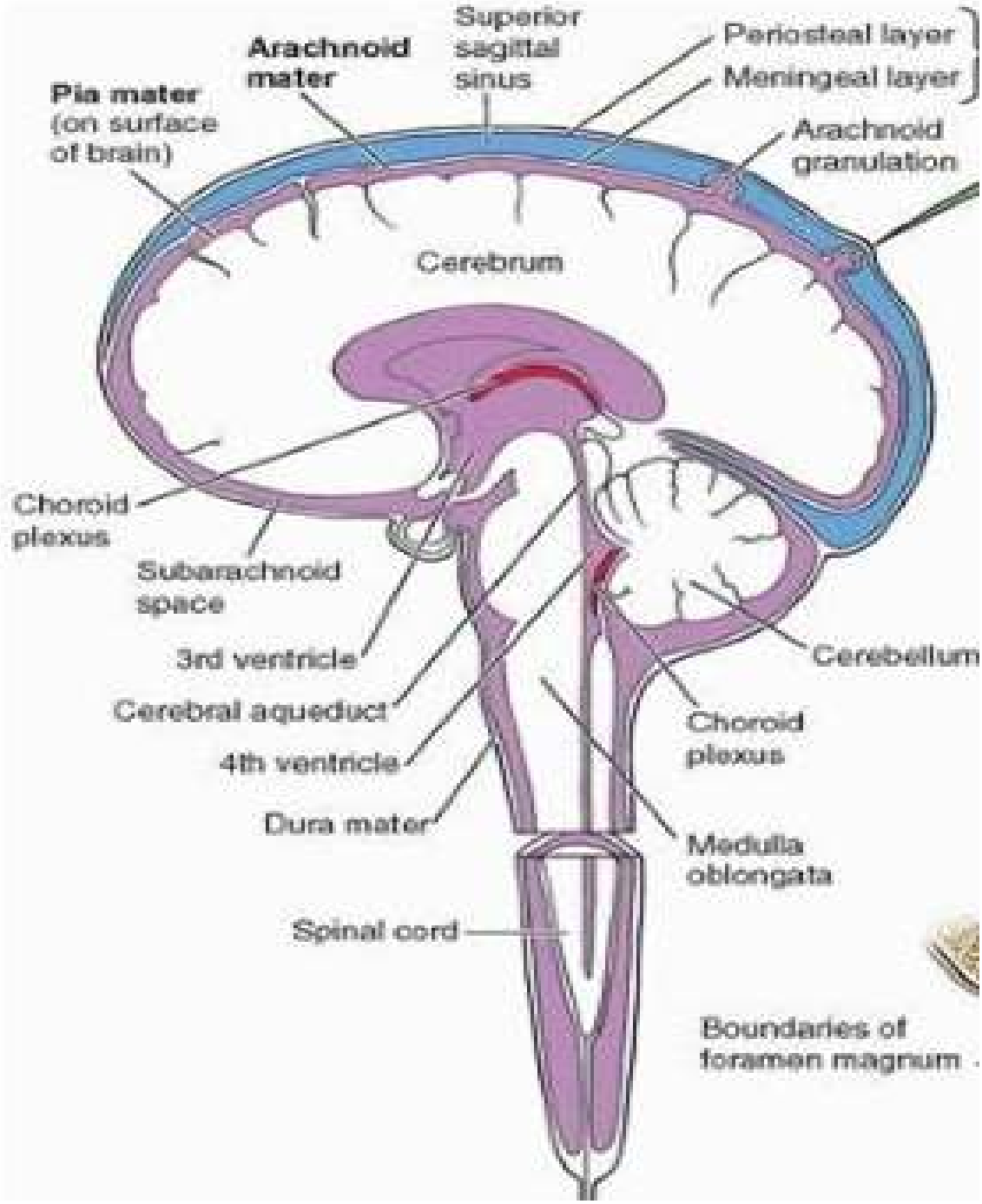
The falx cerebri is the largest in fold of dura in the longitudinal cerebral fissure separates the two cerebral hemispheres. It merges in posterior aspect with the cerebellar tentorium.

The cerebellar tentorium (tentorium cerebelli) is a second largest fold of Dura mater that overlies the posterior cranial fossa. It separates the occipital lobes of cerebral hemispheres from cerebellum. It also supports the occipital lobes.

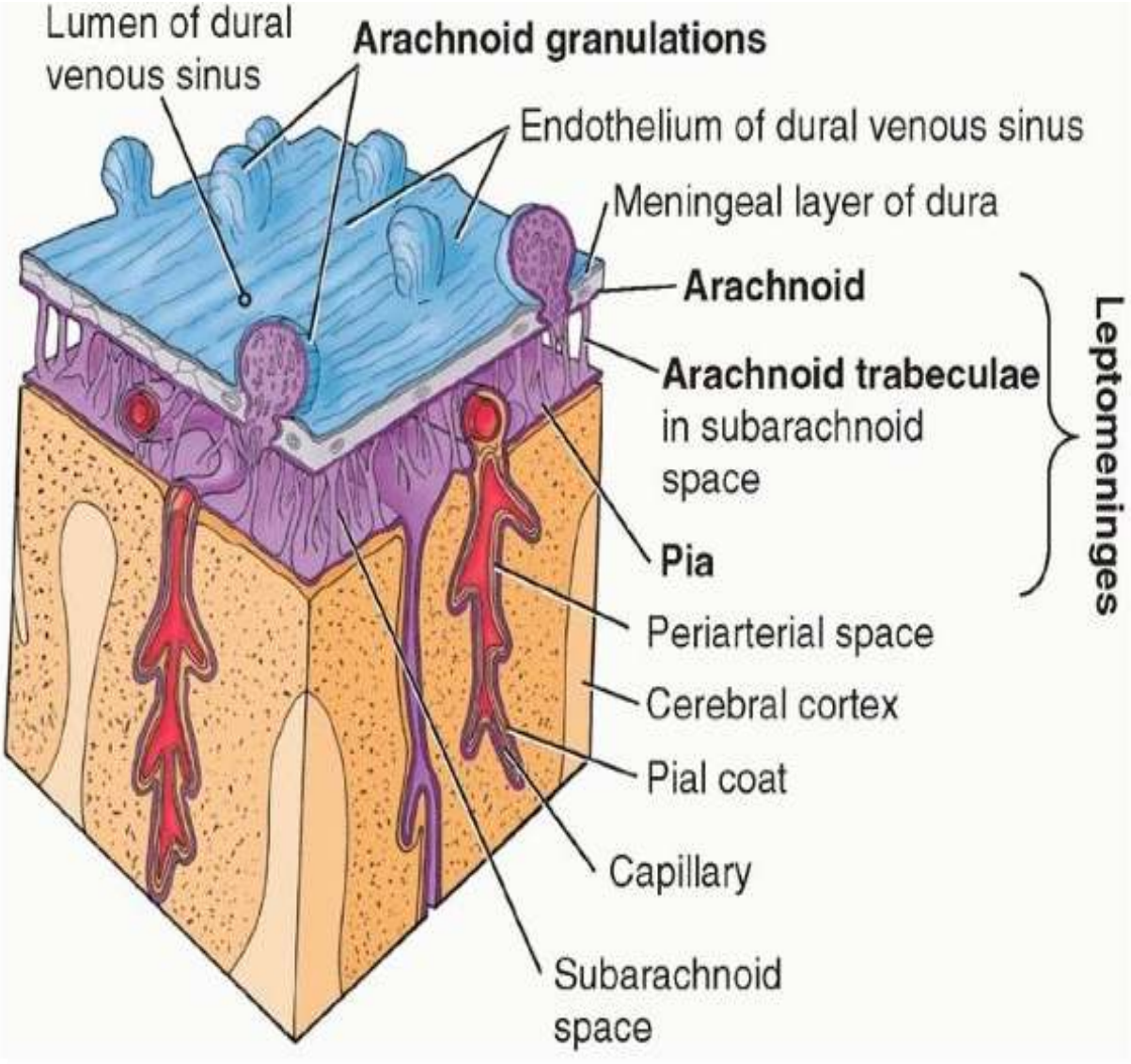
The falxcerebri (cerebellar falx) attaches to cerebellar tentorium and there by supports it. The falx cerebelli is a vertical dura and is attached to inferior part of cerebellar tentorium. The cerebellar falx partially separates the cerebellar hemispheres.

The sellar diaphragm （diaphragmasellae) is a smallest in fold of dura mater and forms partial roof over hypophysial fossa.

This figure shows dural covering and subarachnoid space (purple) around the brain, are continuous with that around the spinal cord:



This figure shows two layers of dura mater separate to form dural venous sinuses:



The dura is innervated by meningeal branches of trigeminal nerve. Other branches are from vagus, C1.C2, C3 nerves and branches from hypoglossal nerve. There are many sensory endings along each side of the superior sagittal sinus and in the cerebellar tentorium which are sensitive to stretching. Pain arising from the dura is generally referred, perceived as a headache (in cutaneous or mucosal regions supplied by the involved cervical nerve). Stimulation of sensory nerve endings above cerebellar tentorium causes referred pain over the same side of head. Sensory nerve endings below the level of the tentorium cerebelli produces referred pain to the back of the neck and scalp along greater occipital nerve distribution.

The vasculature of dura is from the internal carotid arteries, middle meningeal artery branch from maxillary artery, occipital, and small branches from vertebral arteries. The most important branch is the middle meningeal artery. Because it is more prone for damage related to injuries of head.

Arachnoid Mater:

The arachnoid layer is delicate and impermeable covering over the brain. It lays in between two other coverings of brain namely pia mater and dura mater. The subdural space between arachnoid and dura is filled with a small amount of fluid. The subarachnoid space is between pia mater and arachnoid mater which contains with cerebrospinal fluid.

The subarachnoid cisterna is the wide separations between pia mater and arachnoid mater at the point of arachnoid mater bridging over sulci. There are two cisterna one is cerebellomedullaris (between cerebellum and fourth ventricle) and other cisterna interpeduncularis (between cerebellar peduncles). These cisternae are freely connected to one another and with rest of the subarachnoid space.

In some areas the arachnoid mater enters into the venous sinuses forming arachnoid villi which are more around superior sagittal sinus. These arachnoid villi aggregate in some areas to form arachnoid granulations. The main function of arachnoid villi is to drain the cerebrospinal fluid into blood vessels.

There are numerous fibrous strands in subarachnoid space that connect pia mater and arachnoid mater. The cerebral vessels and nerves lie in the space, in case of optic nerve it envelops till its entry into eye ball and finally merges with sclera.

The choroid plexuses are the protrusions of arterial tufts into the ventricle which produce CSF. They are located in 2 lateral ventricles, third and fourth ventricle. The CSF exits the fourth ventricle through the foramina in its roof into the subarachnoid space. Here it baths the surface of brain and spinal cord below and finally diffuses into blood vessels via arachnoid villi.

Pia Mater:

The pia mater is a thinner membrane that is highly vascularised by fine blood vessels. It is adherent to surface of brain and follows the contour of brain (including gyri and sulci) and responsible for the shiny appearance of brain. It forms pial coat and a periarterial space around arteries penetrating the cerebral cortex, and epineurium around nerves. The pia mater also forms the telachoroidea at the roof of third and fourth ventricles, and choroid plexus along with ependymal tissue which protrudes into the ventricles.

Choroid plexus

These are present in ventricular cavities and are lined by ependymal. They are protrusions of tuft of arteries lined by pia mater in the ventricles. They are present in all ventricles largest tuft in lateral ventricle. They produce cerebrospinal fluid. The epithelium of the choroid plexus represents a barrier between the blood and the CSF, the blood-CSF barrier. Thus, many substances that can leave the capillaries of the choroid plexus cannot enter the CSF.

Physiology of cerebrospinal fluid (CSF):

It is called the lymph of brain by Claudebernard. The brain and spinal cord is bathed by CSF in subarachnoid space. The Lipid-soluble substances (CO_2 and O_2) and water, freely cross the blood-brain barrier and equilibrate between blood and CSF. Protein and cholesterol are excluded from the CSF because of their large molecular size.

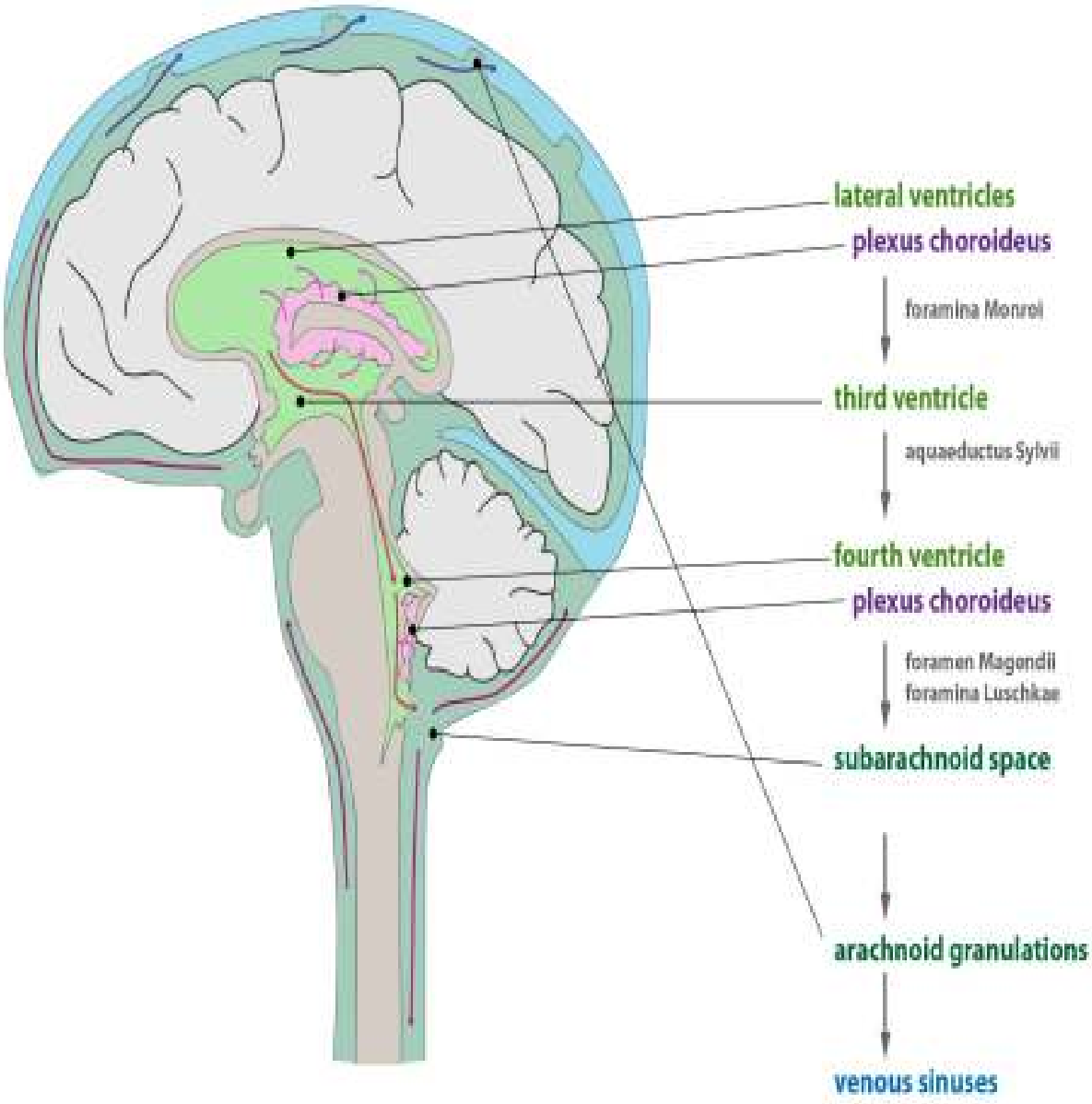
Circulation and Drainage of the Cerebrospinal Fluid

About one-half liter of CSF is produced each day, still the net volume of CSF in the ventricles and the subarachnoid space is 130-140 ml (approximately 25ml is in the ventricles) [7]. In addition, approximately 75 ml surrounds the spinal cord. Thus, the total amount is renewed several times a day .The CSF is produced in the lateral ventricles which enters into the third ventricle through the interventricular foramen of Monro. From there CSF flows to fourth ventricle through the narrow cerebral aqueduct. More CSF formed by choroid plexus is added in the third and fourth ventricles. The fluid enters the subarachnoid space (more specifically, the cisterna magna) through openings in the roof of the fourth ventricle. The openings are named as the foramen of Magendie (one in the midline posteriorly) and the lateral recesses or foramina of Luschka (two laterally in roof of fourth ventricle). The CSF then baths over the entire cerebral surface and spinal cord till second sacral vertebra.

The velocity with which CSF flows is not even, however, as shown by following the spread of injected substances. The direction of CSF from the base of the cerebrum is upwards along the lateral surface of cerebral hemispheres towards midline where most of the fluid diffuses into venous sinuses. This happens by way of small evaginations of the arachnoid—arachnoidvilli—into the venous sinuses.

The diffusion of CSF from subarachnoid space to the venous sinuses is probably caused by a difference in hydrostatic pressure, which is at higher level in the subarachnoid space (about 15 cm H_2O) than in the venous sinuses (7-8 cm H_2O). Some of the CSF is drained along other routes, such as lymphatic vessels in cranial and spinal nerves.

Circulation and Drainage of the Cerebrospinal Fluid



Composition of Cerebrospinal Fluid

The concentration of sodium, potassium, and several other ions is about the same in the CSF as in the blood (there are some minor differences, however). The concentration of glucose is about two-thirds of that in the blood. A major difference concerns proteins: there is normally very little protein in the CSF (less than 0.5% of the plasma protein concentration). Water and soluble substances are freely exchangeable between the CSF and the interstitial fluid of the nervous tissue because the ependyma is freely permeable to water and even small protein molecules. It is not surprising, therefore, that many neurotransmitters, peptides, and other neuroactive substances can be found in the CSF, and their presence there does not by itself signify a functional role. Some substances, however—notably hormones synthesized in the anterior pituitary—are apparently actively secreted into the CSF, not simply accepted by passive diffusion. There is evidence that some other substances use the CSF as a means to reach specific receptors close to the ventricles. We mentioned at the beginning of this chapter that, because the brain almost floats in it, the CSF has important protective functions. This buoyancy reduces the weight of the brain to about 50 g, which means less traction on vessels and nerves connected cerebrum and spinal cord. Furthermore, the effect of blows to the head on

the brain is dampened because water has to be pressed aside before the brain hits its hard surroundings (the skull). Another possible functional role of the CSF can be deduced from the fact, mentioned above, that water and solutes pass freely between it and the extracellular fluid (interstitium) of the nervous tissue. This means that the accumulation of substances in the nervous tissue (such as potassium ions during prolonged periods of intense neuronal activity) may be minimized by diffusion into the CSF. This would be of significance, however, only for neurons that are fairly close to the ventricles. The diffusion of molecules in the labyrinth like brain interstitium is much slower than in free water. Thus, after injecting representative substances in the brain, the concentration is reduced by 90% some 1 to 3 mm away from the injection site.

Regardless of the normal functions of substances in the CSF, examination of the CSF composition gives valuable information of the extracellular fluid of the brain. This fluid compartment is difficult to examine directly, but since the ependyma is freely permeable, one can safely assume that the composition of the CSF matches fairly well the environment of the neurons.

Comparison of Cerebrospinal Fluid (CSF) and Blood Concentrations

CSF ≈ Blood	CSF < Blood	CSF > Blood
Na^+	K^+	Mg^{2+}
Cl^-	Ca^{2+}	Creatinine
HCO_3^-	Glucose	
Osmolarity	Cholesterol*	
	Protein*	
* Negligible concentration in CSF.		

Normal CSF constituents:

Protein-

Ventricular- 5-15 mg/dl

Lumbar- 15-25 mg/dl

Cisternal- 14-45mg/dl

Glucose- 44-100 mg/dl

Chloride- 725-750 mg/dl

Phosphorus- 7.31(at arterial PH of 7.41)

Cells present in CSF- 0-5 cells mm^3 mainly lymphocytes

Enzymes present in CSF- LDH, AST and CPK.

Normal pressure of CSF- 100-200 is cm of H2O.

Functions of CSF

1) Provides buoyancy which reduces the weight of the brain to about 50 g, which means less traction on vessels and nerves connected to the central nervous system.

2) It regulates the intracranial pressure.

3) Supports venous sinuses.

4) Acts as secondary pathway in hormonal transport and distribution.

5) Maintenance of homeostasis and removal of waste products.

6) Acts as buffer and maintains pH, there by regulates respiration.

7) Plays an important role in nutrition and metabolism in CNS.

Types of meningitis:-

Meningitis can be categorized according to CSF cytochemical picture as, neutrophilic meningitis, lymphocytic meningitis, and aseptic meningitis.

Neutrophilic meningitis:

The most common cause is bacterial infection. Other rare causes are fungal infections, nocardia infection, actinomyces infection etc.

Bacterial meningitis:

Acute bacterial infection of meninges causes a clinical picture of acute meningitis. It is often referred as bacterial meningitis or septic meningitis or purulent meningitis. Most often meninges, subarachnoid space and brain parenchyma are all involved in inflammatory reaction causing meningoencephalitis.

Currently most common organisms responsible for community acquired bacterial meningitis are streptococcus pneumonia, meningococcus, Hemophilus influenza, group B Streptococcus and Listeria monocytogenes[1]. Neisseria meningitides and Streptococcus

pneumoniae are the most common pathogens responsible for meningitis in normal individuals (without immune deficiency).

Streptococcus pneumoniae is the most common pathogen responsible for meningitis in adults above 20 years. The predisposing conditions are pneumonia due pneumococcus, sinusitis, mastoiditis, otitis media, cochlear implants, diabetes mellitus, post splenectomy.[2]

Neisseria meningitides is most common in adolescent and young adults (2- 20 years). The bacteria are usually recovered from blood or a cutaneous lesion before meningitis starts, indicating that spread to the CNS is hematogenous. Occasionally it may gain access directly from the nasopharynx through cribriform plate. Found in individuals with complement deficiency including properdin[3].

In infants and children most common organisms are pneumococcus, Neisseria meningitides and Hemophilus influenzae type b.

In infancy most common pathogens are Group *B* Streptococcus, Escherichia coli, Listeria monocytogenes. L.Monocytogenes is frequently reported in meningitis above 50 years, especially adults with chronic diseases *(*e.g. renal disease with dialysis, malignancy, connective tissue disorders).

Staphylococci (S. aureus and S. epidermidis) and gram-negative bacilli are common pathogens in patients following a neurosurgical procedure. Sometimes it is a complication of cavernous sinus thrombosis, subdural or epidural abscess.

Recurrent Bacterial Meningitis signal a host defect, either in local anatomy or in antibacterial and immunologic defenses.

1. Defects in local anatomy, for example:

• Head trauma causing CSF rhinorrhoea due basilar skull fracture.

• Fracture to temporal bone with access of microorganisms from the ear

• In situ shunts (ventriculovenous shunting) for treatment of hydrocephalus.

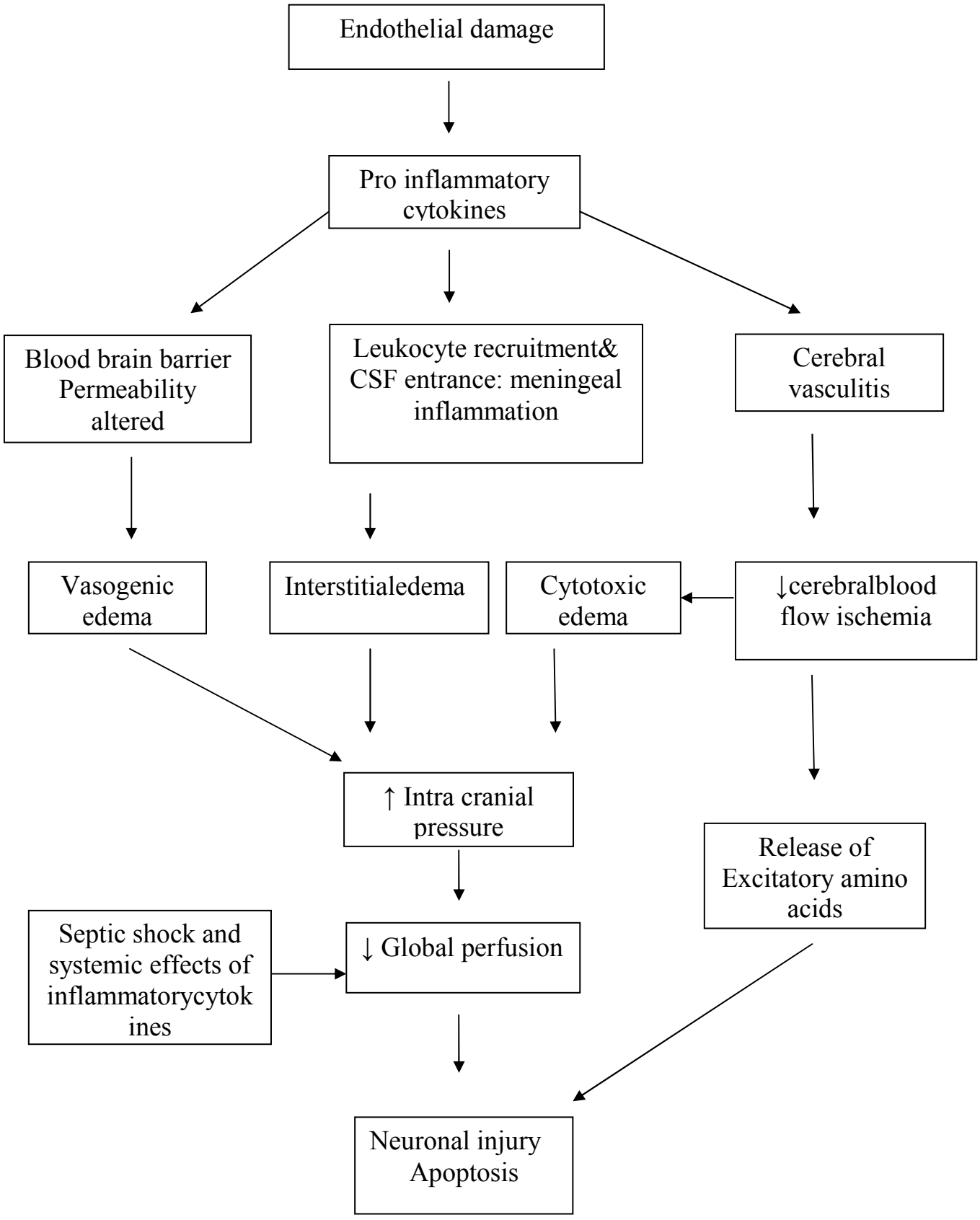
2. General causes (defective immunologic defenses), for example:

• Diabetes mellitus

• Immune deficiency or immune compromised states.

A pathogenesis of bacterial meningitis is inflammatory reaction induced by invading bacteria, most often due elevated CSF cytokines and chemokines [5]**.** The inflammatory reaction is severe in the subarachnoid space over the brain and around the cisterns (base of the brain). It may extend along the perivascular spaces into the brain and spinal cord but rarely breaks into the parenchyma of the brain.

Fig-1: PATHOPHYSIOLOGIC CASCADE IN BACTERIAL MENINGITIS.[36]



The classical clinical triad of meningitis consists of fever, headache and neck rigidity. Nausea, vomiting, phonophobia, photophobia are usually seen. With the disease progression, the sensorium becomes clouded and stupor. Convulsive seizures is often an early symptom (20%-40% cases), especially in children.

The temperature is elevated at 101°F to 103°F. The pulse is usually rapid and there is increased respiratory rate. There is nuchal rigidity, Kernig's sign (resistance offered to leg extension) and Brudzinski's signs (resistance to forward flexion of the neck). The above signs may be absent in newborn and elderly. Tendon reflexes are often decreased. Cranial nerve palsies and focal neurologic defects are uncommon and usually develop several days after the onset of infection. Papilledema may develop if the meningitis persists for more than a week otherwise optic disc is normal.

The WBC count is increased and it is usually in the range of 10,000/mm^3 to 30,000/mm^3. The pressure of CSF is increased and usually between 200 and 500 mm H_2O. The CSF is cloudy because it contains a numerous cells, predominantly polymorphonuclear leukocytes. The cell count in the CSF is usually between 2,000/mm^3 and 10,000/mm^3. The protein content of CSF is increased. The sugar content is decreased (below 20 mg/dl). Particle agglutination testing may rapidly identify bacterial antigens in the CSF.

Another rapid test used in the evaluation of bacterial meningitis is polymerase chain reaction (PCR.) of the CSF. PCR is highly sensitive and specific test for the detection of bacteria in CSF such as Streptococcus Pneumoniae. Other tests include real time PCR for rapid diagnosis of bacterial meningitis. Fluorescence In situ Hybridization (FISH) is also test for rapid diagnosis of bacterial meningitis with high sensitivity but it is not cost effective. FISH is of great use in identification of CSF samples which shows multiple bacteria after staining [6].

Neurological complications and pathological correlation in acute bacterial meningitis:

I. In acute meningeal inflammation:

A. Pure pia-arachnoiditis: headache, stiff neck, Kernig and Brudzinski signs.

B. Subpial encephalopathy: manifests as confusion, stupor, coma, and convulsions.

C. Cranial nerve roots involvement (Inflammatory or vascular): ocular palsies, facial weakness, and deafness.

D. Meningeal vein thrombosis: may present as focal seizures, focal cerebral defects such as hemiparesis. There may be spinal cord infarction.

E. Ependymitis, choroidal plexitis

F. Cerebellar or cerebral hemisphere herniation: causes upper cervical cord compression with quadriplegia or signs of midbrain–third nerve compression.

II. In more sub-acute and chronic forms of meningitis:

A. Tension hydrocephalus, due at first to purulent exudate around the base of the brain, later to meningeal fibrosis, and rarely to aqueduct stenosis.

B. Subdural effusion.

C. Extensive venous or arterial infarction.

III. Late effects /sequelae:

A. Meningeal fibrosis around optic nerves causes blindness and optic atrophy (opticochiasmatic arachnoiditis).

B. Meningeal fibrosis around spinal cord and roots causes spastic Paraparesis with sensory loss in the lower segments of the body (meningomyelitis).

C. Chronic meningoencephalitis with hydrocephalus.

TREATMENT

The mainstay of treatment is appropriate antibiotic therapy targeted to the causative pathogen.

GENERAL PRINCIPLES OF THERAPY— Bacterial meningitis is a medical emergency. Treatment should be started early while waiting for results of specific diagnostic tests. Treatment can be altered according to the laboratory findings thereafter.

The general requirements for choosing an antibiotic therapy for bacterial meningitis are[14]**:**

- Antibiotics which are bactericidal for the suspected infecting organism.
- Antibiotics which is able to enter the CSF.
- Based on pharmacodynamic characteristics of the antimicrobial agent, the antibiotic regimen with optimal bactericidal effects is selected.

Choice of antibiotic regimen — Antibiotic selection should be empirical and started soon after CSF is obtained for diagnostic testing or in instances of delayed lumbar puncture. The antibiotic is directed at the most likely bacteria based on age of the patient and associated comorbid illness in such patients. To assess susceptibility patterns also may be important.

Depending upon the available CSF Gram staining results, the antibiotic selected should cover the most likely causative pathogen. In case of negative of gram staining results but CSF analysis results are consistent with the features of acute bacterial meningitis, the empirical antibiotic regimen should be continued.

EMPIRICALTHERAPY — The selection of antibiotic in patients with suspected acute bacterial meningitis is targeted towards most likely bacteria which is based on the age of patient and host factors[15]. There are no documented randomized trials regarding the empiric therapy for bacterial meningitis in adult patients. Hence, empirical therapy guidelines are based on randomized trials in children, in vitro bacterial susceptibility and pharmacodynamic data, and clinical experience.

The third-generation cephalosporins like ceftriaxone and cefotaxime are the beta-lactam antibiotics of choice in the empirical therapy of acute bacterial meningitis. These antibiotics have been

superior to chloramphenicol and cefuroxime based on randomized trials in children affected from bacterial meningitis[16,17,18]. These beta-lactam antibiotics easily cross blood brain barrier and have relatively better CSF penetration and potent bactericidal activity against the most common pathogens responsible for majority cases of bacterial meningitis, with some exceptions like L. monocytogenes and few penicillin- resistant S. pneumoniae strains [19,20,21]. Since there is increase in the prevalence of penicillin-resistant pneumococcus strains, vancomycin must be combined with third-generation cephalosporins (ceftriaxone or cefotaxime) as empirical therapy until culture and sensitivity results are available[22].

EMPIRICAL therapy includes.

- Cefotaxime — 2 gram intravenous every 4 to 6 hours.

  OR

- Ceftriaxone — 2 gram intravenous every 12 hours.

  PLUS

- Vancomycin — 30 to 60 mg per kg IV per day (2 or 3 divided doses).

  PLUS

- In adult patients age more than 50 years, ampicillin — 2 gram intravenous every 4th hourly.

Empirical therapy of bacterial meningitis

AGE OF PATIENT	ANTIMICROBIAL THERAPY"
0-4 weeks	Cefotaxime plus ampicillin
0-4 weeks	3rd generation cephalosporins + ampicillin (plus dexamethasone)
3 months-18 years	3rd generation cephalosporins + vancomycin (±ampicillin)
18-50 years	Third-generation cephalosporins + vancomycin (±ampicillin)
>50 years	3rd generation cephalosporins + vancomycin with ampicillin
Immunocompromised individuals	Vancomycin plus ampicillin and Ceftazidime
Basilar skull fracture	3rd generation cephalosporin + vancomycin
Head trauma; neuro-surgery	Vancomycin plus Ceftazidime
CSF shunt	Vancomycin plus Ceftazidime

Impaired cellular immunity

The patients on cytotoxic chemotherapy, lymphoma patients or patients on high-dose corticosteroids or any causes leading to defective cell mediated immunity, antibiotic coverage must be directed against L.Monocytogenes, pneumococcus[23] and Pseudomonas aeruginosa.

The appropriate antibiotic regimen for patients with adequate renal functions is:

- Vancomycin — 30 to 60 mg per kg per day intravenous (2or 3 divided doses).

  PLUS

- Ampicillin — 2 gram intravenous every fourth hourly.

  PLUS ANY ONE BELOW

- Cefipime — 2 gram intravenous every eighth hourly.

  OR

- Meropenem — 2 gram intravenous every eighth hourly.

Nosocomial meningitis:

Empirical therapy for nosocomial meningitis should be directed to cover both gram-positive bacteria and gram-negative bacteria (mainly

Pseudomonas aeruginosa and Klebsiella pneumoniae).

The appropriate antibiotic regimen in patients with adequate renal functions is:

- Vancomycin — 30 to 60 mg per kg per day IV (in 2 or 3 divided doses).

  PLUS

- Ceftazidime— 2 gram intravenous every eighth hourly.

  OR

- Cefipime— 2 gram intravenous every eighth hourly.

  OR

- Meropenem — 2 gram intravenous every eighth hourly.

Beta-lactam allergy:

The antimicrobial therapy in patients with drug allergies is challenging. The importance of beta-lactam antibiotics in the treatment of acute bacterial meningitis has to be considered. One option is to patient can be desensitized who has a history of an anaphylaxis to beta-lactam antibiotics and who need treatment with this group of antibiotics. Consecutively, an alternate treatment regimen should be used while the

patients with drug allergy are being desensitized. The indication for desensitizing a patient must be based on the Grams staining and/or culture and susceptibility results.

For empirical treatment in patients with profound beta-lactam antibiotic allergies, one of the following regimens can be started.

- Vancomycin — 30 to 60 mg per kg per day IV (in 2 or 3 divided doses).

  PLUS

- Moxifloxacin — 400 mg intravenous OD

  PLUS

- If Listeria monocytogenes coverage is needed (in patients more than 50 years and or in patients with impaired cell- mediated immunity), intravenous trimethoprim-sulfamethoxazole 10 to 20 mg per kg per day (of the trimethoprim component) in divided doses (every six to twelve hours).

Specific antibiotic therapy for acute bacterial meningitis:

MICRO-ORGANISM	STANDARD THERAPY	ALTERNATIVES
Haemophilus influenzae		
• β-lactamase-negative	Ampicillin	3rd generation cephalosporin; chloramphenicol.
• β -lactamase-positive	3rd generation cephalosporin	Chloramphenicol; cefepime.
Neisseria meningitidis	Penicillin G or ampicillin	Third-generation cephalosporin; chloramphenicol.
Streptococcus pneumoniae		
• Penicillin(sensitive)	Penicillin G or ampicillin	3rd generation cephalosporins; chloramphenicol.
• Penicillin(intermediate sensitivity)	3rd generation cephalosporins	Vancomycin; meropenem.
• Penicillin(resistant)	Vancomycin plus 3rd generation cephalosporin.	Meropenem

MICRO-ORGANISM	STANDARD THERAPY	ALTERNATIVES
Enterobacteriaceae	3rd generation cephalosporin	Meropenem; fluoroquinolone; trimethoprim/sulfamethoxazole, or cefepime.
Pseudomonas aeruginosa	Ceftazidime or cefepime.	Meropenem; fluoroquinolones; pipericillin.
Listeria monocytogenes	Ampicillin or penicillin G.	Trimethoprim/sulfamethoxazole .
Streptococcus agalactiae	Ampicillin or Penicillin G.	3rd generation cephalosporins; vancomycin.
Staphylococcus aureus		
• Methicillin-sensitive	Nafcillin or oxacillin.	Vancomycin.
• Methicillin-resistant	Vancomycin.	Linezolid, quinupristan-dalfopristan, daptomycin.
Staphylococcus epidermidis		Vancomycin

- **Role of Dexamethasone in treatment of bacterial meningitis**:

Initial studies had demonstrated that there was early resolution of symptoms and CSF inflammatory parameters and decreased mortality with addition of dexamethasone to the regimen but the difference was not statistically significant.

A meta-analysis studied by Van de Beek MD et al initially concluded that the benefit of Dexamethasone as adjunctive for bacterial meningitis patients remains unproven[24]. Recently the trial by deGans and van de Beck has shown a reduction in death rates and improved overall outcome if dexamethasone (10 mg) is given before the first dose of antibiotics and every 6 hourly for four days. In children, fever subsided more rapidly and the incidence of sensorineural deafness and other neurologic complications were reduced (particularly in children's suffering from H. influenza meningitis).Hence the treatment of childhood meningitis include high dose dexamethasone (0.15 mg/kg four times daily for 4 days), administered as early as possible.

Studies by Tunkel and Scheld suggested the use of the glucocorticoids if there is septic shock. They favour the use of glucocorticoids in patients with severe infection at any age (very high CSF pressure or signs of herniation, high CSF bacterial count, and signs of acute adrenal insufficiency seen in Neisseria meningitides).

Supportive measures

- Fluid replacement —Management of fluid and electrolyte balance should be done cautiously, since both over-correction and under-correction may have adverse effects.

- Reduction of raised intracranial pressure — Patients suffering from acute bacterial meningitis who are stuporous or comatose, who have very high intracranial pressure, may benefit by inserting an intracranial pressure monitor device[25].

  Intracranial Pressure more than 20 mm Hg must be treated. There is a rationale that even little elevations of intracranial pressure (more than 15 mm Hg) should be treated to avoid cerebral herniation and irreversible brainstem injury following larger elevations of intracranial pressures:

  - Methods to reduce intracranial pressure include head end elevation to 30 degrees.

  - Hyperventilation to maintain PaC02 in the range of 27 - 30 mm Hg.

  - Use of hyperosmolar agents reducing intracranial pressure may increase the survival in bacterial meningitis[26].

Prognosis — There is an appreciable mortality rate associated with bacterial meningitis even with the administration of appropriate antibiotics.

Lymphocytic meningitis:

Tuberculosis is the most common cause of lymphocyte predominant meningitis especially in developing countries. Other causes of lymphocytic meningitis are syphilis, Lyme disease, brucellosis, Cryptococcosis, and other fungal infection. All these cause sub-acute or chronic form of meningitis.

Out of all the above causes, tuberculosis remains a major problem to public in health sector mostly seen in age group of 15-59 years. In developed countries as well[1], there is a high probability for re-emergence of tuberculosis as a significant public health problem due to increasing incidence of human immune deficiency virus (HIV). The incidence among patients with full-blown AIDS is almost 500 times the incidence in the general population for tuberculosis. (Pitchenik et al).

The central nervous system tuberculosis contributes about 5-10% of all tuberculosis. Among the central nervous system manifestations, tuberculosis, meningitis is the most common (70-80percent) followed by tuberculoma[28].

Risk factors for the tuberculosis meningitis are recent acute infectious disease in children, chronic alcoholism, diabetes mellitus, malignancy, long term glucocorticoids therapy and AIDS[29].

The most common organism responsible for tuberculous meningitis is mycobacterium tuberculosis. Mycobacterium bovis related meningitis is seen in less than 5% of cases[28]. Very few cases of tuberculous meningitis due to Non tuberculous mycobacterium have been reported inspite of increased frequency of Mycobacterium avium intracellulare in AIDS patients[30].

Pathogenesis

Tuberculous meningitis arises as a complication of Tuberculosis elsewhere in the body even though extra cranial focus for infection is not identifiable. The evolution of tuberculous meningitis is described in two stages by Rich. They are:

i) Initial seeding in the brain or meninges by haematogenous dissemination of bacilli during primary infection or later due to rupture of caseous granuloma.

ii) Rupture of one of the above subpial caseous tuberculous focus/foci in brain is called Rich Focus.

The other mechanisms of tuberculous meningitis include:

a) Haematogenous dissemination during Primary infection or miliary tuberculosis.

b) Direct extension from nearby extra cranial sites like mastoiditis tuberculosis of spine or skull bones.

c) Intracranial lymphatic spread from cervical lymph nodes.

Pure spinal tuberculous meningitis results from rupture of intramedullary tuberculous focus into the subarachnoid space which may be from extension of intracranial meningitis or secondary to tuberculous spine.

Pathology

Pathologically tuberculous meningitis is a meningoencephalitis rather than pure meningitis because infection is not confined to the subarachnoid space but usually penetrates the pia mater and ependyma and enters the underlying brain parenchyma. Pathologic process is characterized by basal meningitis, where a thick, gelatinous exudate accumulates. This exudate obliterates the pontine and interpeduncular cisterns. The process extends up to the meninges around the medulla, the floor of the 3rd ventricle and subthalamic region and the under surfaces of

temporal lobes .The three pathologic features of tuberculous meningitis are:

a) Inflammatory meningeal exudate

b) Vasculitis of arteries traversing the exudate.

c) Disturbance of cerebrospinal fluid flow causing hydrocephalus.

Hydrocephalus is seen in patients who always survive more than 4 to 6 weeks. It can be asymmetrical or symmetrical.

Hydrocephalus develops early, more frequent and severe in children compared to adults[31].

Microscopic examination shows the meningeal tubercles, consisting of a central area of caseation surrounded by epithelioid cells and giant cells, plasma cells, lymphocytes, and connective tissue.

Immune complexes were found in a several number of tuberculous meningitis cases indicating the antigen antibody reaction and hypersensitivity reaction plays very significant role in pathogenesis of various symptoms.

Clinical features

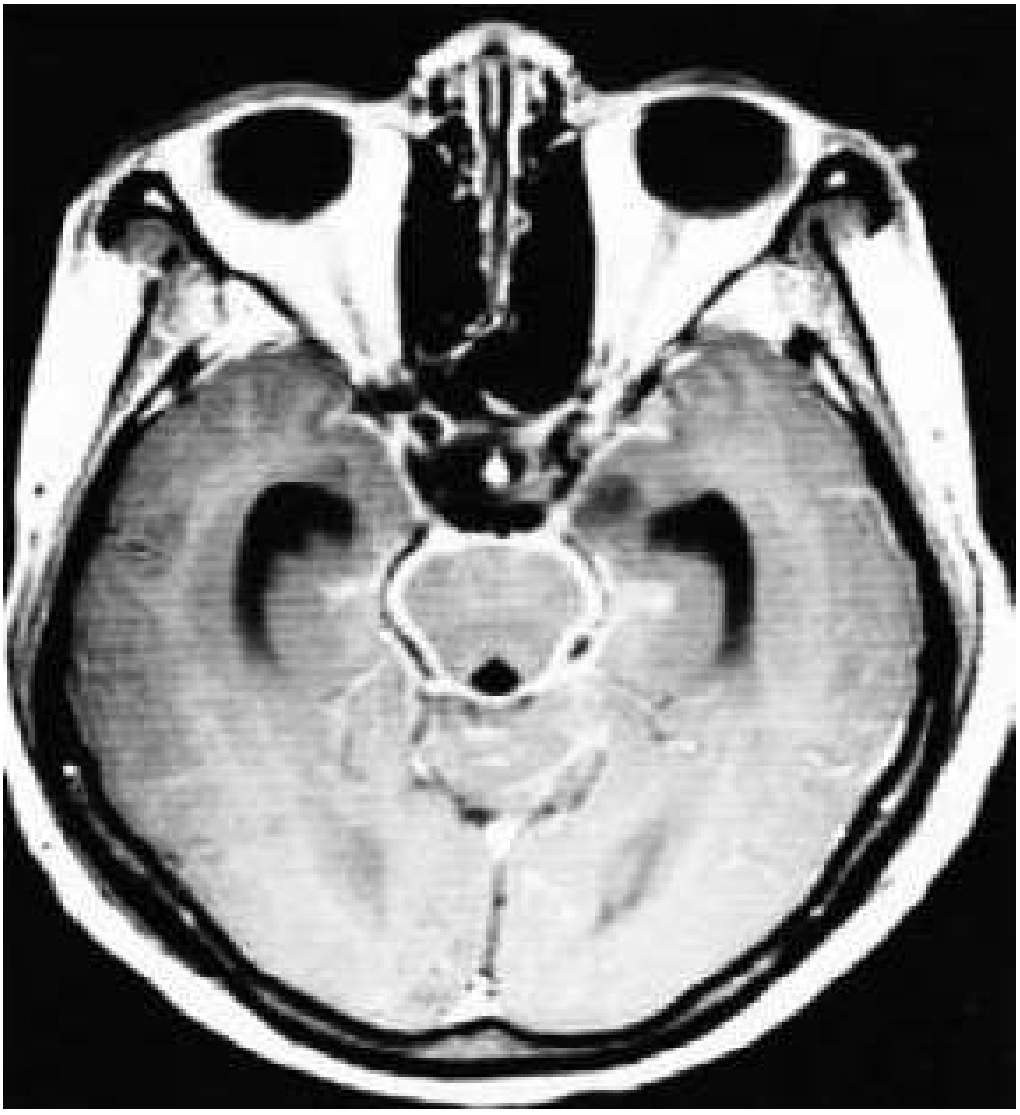
The early manifestations of tuberculous meningitis are low grade fever, headache (50% cases), malaise, confusion and nuchal rigidity (75% cases). Kernig sign and Brudzinski sign may be present. The symptoms evolve slowly over a period of time in case tuberculous meningitis. In case of children and infants irritability, vomiting and seizures are usual symptoms. Neck rigidity is often absent.

Due to chronicity of disease process the cranial nerve palsies and papilledema may be seen at the time of presentation to hospital. The rapid onset of clinical symptoms and focal neurological deficits points towards haemorrhagic infarction.

In 75 percent of cases with tuberculous meningitis there may be a evidence of tuberculosis of others organs/parts of body such as lung (most common), small bowel, bone, kidney.

Untreated cases progress to deepening stupor, cranial nerve palsies, focal neurological deficits, raised ICP. Fatal outcome is expected in 4 to 8 weeks from the day of onset if the infection is left untreated.

MRI (gadolinium enhanced) in tuberculous meningitis. There is contrast enhancement of the basal meninges.



Medical Research Council (MRC) staging of TBM [32,33]

a) Stage 1: Prodromal phase without any neurological symptoms or signs.

b) Stage 2: Stage where Signs of meningeal irritation with or without clouding of consciousness develops and cranial nerve palsies (minor) or neurological deficits.

c) Stage 3: Severe clouding of consciousness, stupor, coma, convulsions, gross paresis or involuntary movements.

Diagnosis

Initially the clinical suspicion supported by careful CSF analysis is the only method followed even today for the diagnosis of tuberculous meningitis.

CSF analysis plays an important role in the diagnosis of tuberculous meningitis. Opening pressures are often but not always elevated[34].

The typical CSF finding in tuberculous meningitis is clear, colourless fluid and may show a cobweb clot on standing. On standing, high levels of protein in CSF can make it appear xanthocromic. The CSF protein levels usually range from 100-500 mg%[35]. Initially if the levels are more than 300mg%, it correlates with poor prognosis. In advanced xanthochromia can develop with protein content of 1000-1500mg% which may be due to spinal block.

CSF glucose level is usually below 40mg / dl or 50% of the parallel blood glucose value. In comparing with bacterial meningitis glucose level is never as low or absent as seen in pyogenic meningitis[36]. Most often CSF sodium and chloride are reduced because of inappropriate ADH

secretion or an addisonian state due to tuberculosis of the adrenal glands. CSF chloride is of not much diagnostic or prognostic significance.

Microscopically CSF examination reveals pleocytosis usually less than 500 cells per mm^3. Among them, predominant cells are lymphocytes. In the early stages polymorphonuclear cells predominate which is replaced by lymphocytes over a period of weeks if untreated.

Like the clinical picture CSF responses may be atypical. CSF changes are dependent on the degree of sensitivity of the patient and the amount of tuberculin in CSF. The CSF picture initially may be normal or mimic pyogenic meningitis. Rarely hemorrhagic CSF has also been recorded which is because of subarachnoid hemorrhage.

In patients with AIDS suffering from tuberculous meningitis CSF protein levels may be normal and may be occasionally acellular[37].

Confirmatory diagnostic tests for tuberculous meningitis include (tests based on detection of the mycobacterium):

i) CSF smears for AFB

ii) CSF culture for AFB

Demonstration of AFB in CSF sample is the single most important test for a definitive diagnosis of presence of tuberculous meningitis.

Limitation is that the procedure is inconsistent and often too slow for immediate therapeutic decisions. CSF smear for AFB is positive in only 5-37% cases and the CSF culture for AFB is positive in 40-80% cases [38, 39].

It is estimated that for demonstration of AFB on smear, bacterial load of 10,000 AFB per ml is required and for culture to be positive, there shall be 100 bacilli per ml of CSF.

It is tedious and time consuming to grow tubercle bacilli on culture. Routine methods require 3 to 8weeks. The radiometric methods are much quicker and give results within a few days.

Varieties of PCR methods are available for detection of specific sequences of Mycobacterium tuberculosis and even other mycobacteria.

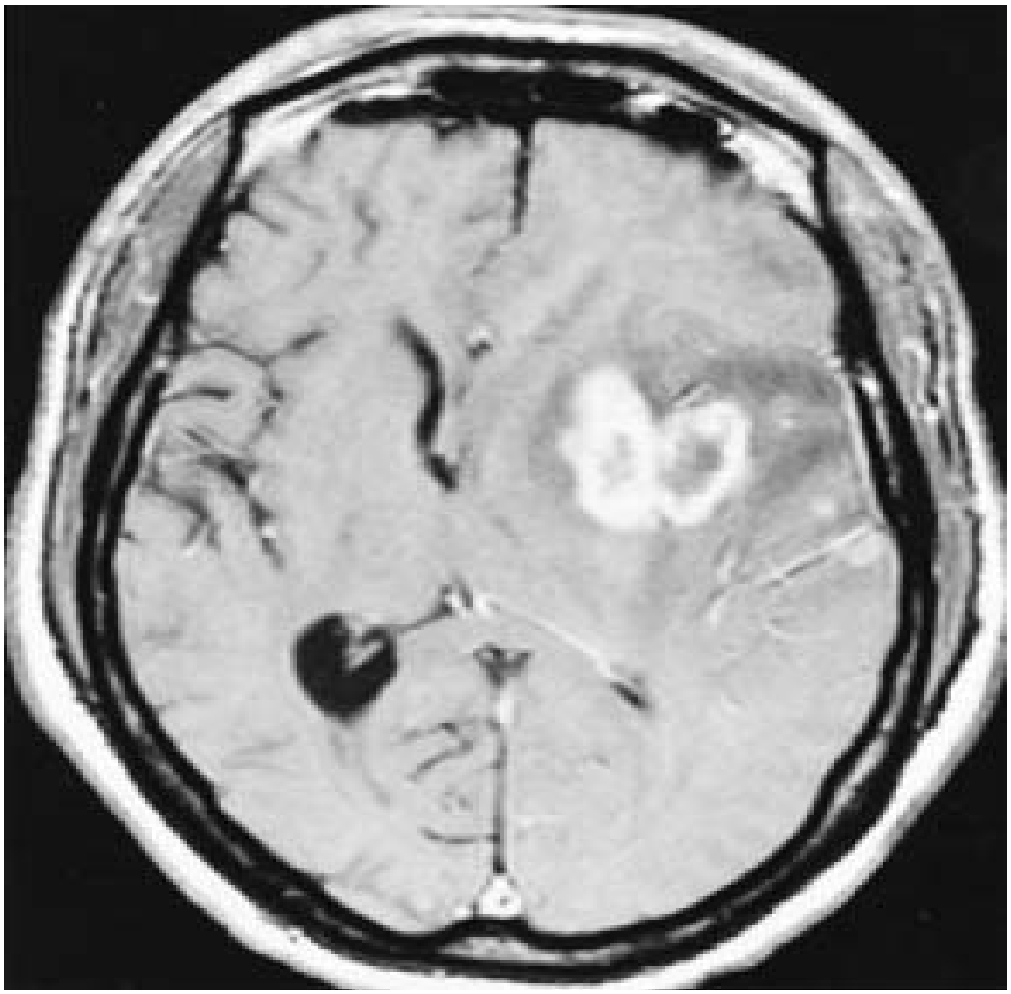
A PCR assay for detection of Tuberculosis is commercially available [43] . This assay is reproducible, sensitive and specific[41].

As compared to 5-20% positivity by AFB staining and mycobacterial cultures, PCR has been found to be positive in 50-70 % of CSF samples from cases having cardinal features of disease as well as biochemical/cytological evidence of neurotuberculosis[42,43,44].

Newer indirect tests for diagnosis of tubercular meningitis

Test	Sensitivity	Specificity	Required time
Radio labeled partition test	90% to 94%	88% to 96%	48 hours
CSF ADA level	73% to 100%	71% to 99%	≈ 24 hours
CSF tuberculostearic acid level	95%	99%	≈ 24 hours
CSF mycobacterial antigen	79% to 94%	95% to 100%	≈ 24 hours
CSF mycobacterial antibody	27% to 100%	94% to 100%	≈ 24 hours
PCR	83% to 100%	80% to 100%	≈ 24 hours

Other diagnostic methods like CT or MRI may be needed in patients who have features of raised intracranial pressure, hydrocephalus, or focal neurologic deficits. Sometimes one or more tuberculoma may be seen. MR angiography may show vascular occlusion from granulomatous infiltration of the vessel walls (arteries of the circle of Willis and their initial branches).



Tuberculoma in the deep parenchyma of parietal hemisphere

Other forms of CNS Tuberculosis are:

- Tuberculous serous meningitis
- Tuberculoma
- Myeloradiculitis

Management

It is very important to treat tuberculous meningitis as early as possible to prevent neurological sequelae and mortality**.** With proper early treatment the disease is treatable and preventable.

Chemotherapy

Based on drug efficacy and toxicity the anti-tubercular drugs are classified into first-line and second line drugs. The first line anti-tubercular drugs are rifampin(R), isoniazid (H), pyrazinamide (Z), ethambutol (E), and streptomycin(S). Second line agents are para-aminosalicyclic acid, ethanolamine, cycloserine, kanamycin, capreomycin and amikacin. Newer second line agents like fluoroquinolones (ciprofloxacin or ofloxacin) and macrolides (clarithromycin and azithromycin) are used in multidrug resistant (MDR) cases and in case of intolerant first line agents. Isoniazid, pyrazinamide, and ethambutol have better CSF penetration compared to others drugs.

Treatment regimens

The pharmacotherapy consists of combination of anti-tubercular drugs. World Health Organisation has recommended the use of four anti-tubercular drugs (HRZE) for 2 months followed by two drugs (HR) for next 6 to 7 months in the treatment of tuberculous meningitis. The above

same regimen is followed for tuberculoma and spinal disease. The current United Kingdom guidelines recommends for 12 months anti-tubercular regimen in uncomplicated cases of tubercular meningitis. The American Thoracic society recommends a course of 2 months of HRZE, followed by 4 months of HR and in case of children for 10 months. A recent study in South India has inferred that directly observed treatment, short course (DOTS) is effective regimen in neurotuberculosis. (Venugopal etal Indian J of Tb).

Recommended anti-tuberculosis (first line) drugs:

Drug	Usual Daily dosage	Adult dosage
Isoniazid (H)	5 to 10 mg/kg	300 mg
Rifampin (R)	10 to 12 mg/kg	450 to 600 mg
Pyrazinamide (Z)	25 to 30 mg/kg	1 to 1.5 gram
Ethambutol (E)	15 to 25 mg/kg	800 mg
Streptomycin (S)	15 to 20 mg/kg	0.75 to 1 gram

Multidrug-Resistant (MDR) Neurotuberculosis

Exact incidence of MDR neurotuberculosis is not known due to difficulty in isolating mycobacterium from CSF. The prevalence of MDR in other forms of tuberculosis is 13%. Most commonly MDR tubercular meningitis is seen in immunocompromised patients due to HIV infection. The organism should be isolated and tested for drug sensitivity. At least 2 sensitive drugs should be continued for a full course of 18 to 20 months.

Role of corticosteroids in neurotuberculosis

Indications	
Clinical	i. Stage 2 or 3 disease ii. Raised intra-cranial pressure iii. Focal neurological deficit iv. Tuberculous encephalopathy
Radiological	i. Cerebral or perilesional oedema ii. Hydrocephalus iii. Infarcts iv. Opto-chaismaticar achnoiditis
CSF	Rising CSF protein suggesting spinal block

Dosage and duration:

Adults: Prednisolone -60 mg/day or 1 mg/kg/day.

Dexamethasone- 8 to 16 mg/day.

The drugs are administered for 3 to 6 weeks, and then slowly tapered over 2 to 4 weeks depending upon the clinical response.

Surgical intervention in tuberculous meningitis

Progressive hydrocephalus refractory to medical line of treatment or deterioration of conscious level is the urgent indications for CSF diversion by ventriculo-peritoneal shunt (VP). Surgical excision of tuberculoma is indicated in cases of optic pathway compression resulting in visual impairment, Spinal cord decompression in tuberculosis of spine causing spondylitis.

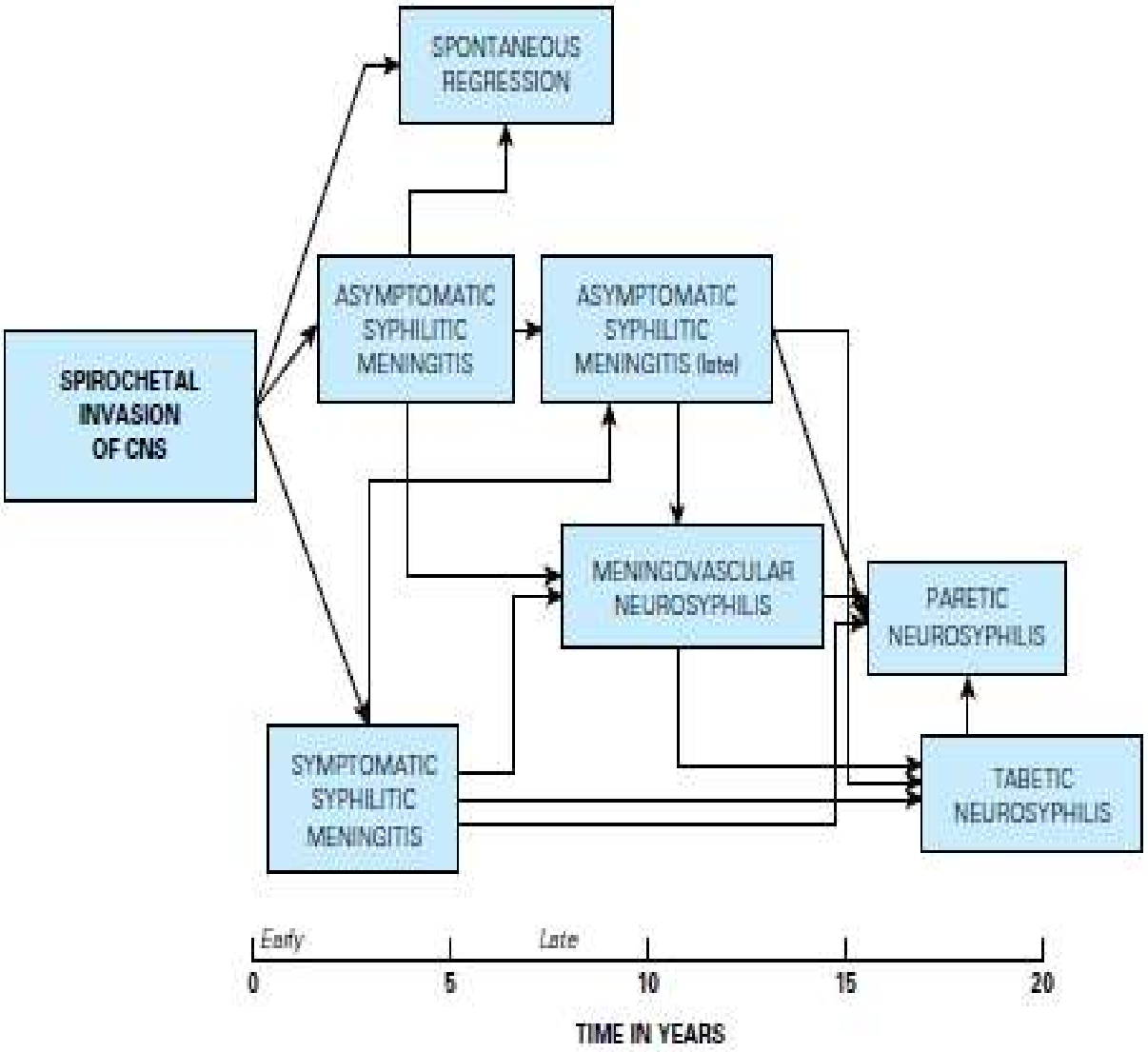
Prognosis

The important factor is clinical stage at commence of treatment. Other important prognostic factors are extremes of age and co existing miliary tuberculosis. Children are more prone for sequelae (25 to 50 % of cases), which include mental regression, behavioral abnormalities, seizures, visual and auditory impairment, cranial nerve palsies, movement disorders, hemiparesis or Para paresis or quadriparesis.

Syphilitic meningitis

Meningeal syphilis, meningovascular, and parenchymal syphilis forms the major clinically symptomatic syphilis.

Evolution of Neurosyphilis



Meningeal Syphilis

Symptoms of meningeal involvement often develop within the first 2 years. The most common symptoms are headache, nuchal rigidity, cranial nerve palsies, seizures, and altered sensorium. The patient is afebrile, unlike the case in tuberculous meningitis. The symptoms vanish over a period of days to weeks.

Meningovascular Syphilis

It is the most common type of neurosyphilis .This type of disease is considered when a young individual has one or more cerebrovascular accidents (35 %), the sudden development of hemiplegia, aphasia, sensory loss and visual impairment. The clinical syndrome occurs 6 to 7 years after the original infection, but sometimes as early as nine months or 10 to 12 years late.

The CSF findings are an elevated cell count, elevated protein, and gamma globulin plus a positive serological test.

Most common site of infarction is in the distal territories of medium and small-caliber lenticulostriate branches *(Heubner arteritis*), of the middle and anterior cerebral arteries. Most characteristic feature is internal capsular lesion, extending to basal ganglia followed by lesions adjacent to the lateral ventricles. Small, benign lesions are usually seen in the caudate nucleus and lenticular nucleus.

Syphilitic Meningoencephalitis (Paretic Neurosyphilis General Paresis, Dementia Paralytica

The general setting of this form of cerebral syphilis is a long-standing meningitis; as remarked above, some 15 to 20 years usually separate the onset of general paresis from the original infection.

Since syphilis is acquired mainly in late adolescence and early adult life, the middle years (35 to 50) are the usual time of onset of the paretic symptoms.

The clinical picture in its full blown disease includes dysarthria, dementia, myoclonic jerks, action tremor, seizures, hyperreflexia, Babinski signs, and Argyll-Robertson pupils (ARP) [47]. Other symptoms are hemiplegia, hemianopia, cranial nerve palsies, and convulsions. The prominent focal signs of unilateral frontal or temporal lobe disease may be prominent (Lissauer's cerebral sclerosis).

The blood serology for the organism is positive in most of the cases. The CSF is abnormal in most of the cases, usually with 10 to 200 cells/mm^3 (lymphocytes, plasma cells, and mononuclear cells); a total protein of 40 to 200 mg/dl; an elevated gamma globulin. The gamma globulin (oligoclonal IgG) represents a specific antibody response to the pathogen.

The pathologic changes are thickening of meninges, cerebral atrophy, enlarged ventricles enlargement, and granular ependymitis. Microscopic examination shows perivascular lymphocytosis, plasma cells, and mononuclear cells; there are many rod-shaped microgliacytes and enlarged astrocytes in parts of the cortex in the place of neuronal loss; mononuclear cells show iron deposition. The findings are more obvious in in the frontal and temporal lobes. Meningeal fibrosis leading to obstructive hydrocephalus is present in several cases.

The prognosis in early treated cases is fairly good; 35 to 40 % of patients made some occupational readjustment; in another 40 to 50%, the disease was arrested but the patient was left dependent.

Diagnosis:

CSF abnormalities like pleocytosis and reactive CSF VDRL tests supporting the clinical evidence are basis for diagnosis. The CSF VDRL is the gold standard for diagnoses[48]. The treponemal antibody tests, such as CSF fluorescent treponemal antibody absorption test are more sensitive.

Treatment of Neurosyphilis (CDC guidelines) [49]

Recommended regimen	
Adults	Aqueous crystalline penicillin G. Dose: 18-24 MU IV/day in divided doses or continuous infusion for 10 to 14 days.
Children	Aqueous crystalline penicillin G, 2 to 3 lakhs/kg/day, given as 50,000 U/kg IV every 4-6 hours for 10 days.

Alternative treatment regimen for adults:

Procaine penicillin, 2.4 Million units intramuscular once daily along with oral probenecid 500 mg in 4 divided doses for a period of 10 to 14 days.

Alternative drugs (for individuals allergic to penicillin):

Doxycycline: 100 mg orally BD for 14 days.

Tetracycline: 500 mg orally QID for 14 days.

Erythromycin: 40mg/kg/day orally QID for 14 days.

Cryptococcal meningitis

Cryptococcosis (*torulosis*) is one of the most commonly encountered fungal infections of the CNS. The organism causing is Cryptococcus neoformans. The organism is a soil fungus found in the birds' droppings (especially pigeons). The respiratory tract is the common port of entry for organism, in some occasions the skin and mucous membranes.

CNS Cryptococcosis has many distinctive clinical Features. The most common early complaints are headache, nausea, and vomiting; altered sensorium is present in about 50% cases[50]. Some patient presents with symptoms of gradually increasing intracranial pressure due to hydrocephalus (Papilledema is seen 50% cases) or with an altered sensorium, dementia, cerebellar ataxia, or Paraparesis (spastic). A pure motor hemiplegia, like that due to hypertensive lacunae, has been the most common type of stroke due to meningovascular lesions.

Predisposing factors are the diseases that supress immunity such as Lymphoma (Hodgkin disease), leukaemia, carcinoma, tuberculosis, and other debilitating conditions in 50% cases. It has been estimated that 6 to 12% of AIDS patients are vulnerable to Cryptococcal meningoencephalitis.

Laboratory investigations:

The CSF shows a varying lymphocytic pleocytosis, (less than 50 cells/mm^3), except in patients with AIDS where there might be few or no cells seen (75% have 5 or less cells /mm^3). The initial CSF picture of polymorphonuclear cells is rapidly changed to a lymphocytic predominance. The glucose is reduced in 75% of cases except in AIDS patients where it might be normal. The protein may reach high levels. Diagnosis is confirmed by finding the organism or its antigens in the CSF. Rapid diagnostic tests like Latex agglutination test that detects Cryptococcal polysaccharide antigen in CSF are widely available (specificity of 90%).

Treatment

Amphotericin B, 0.5 to 0.7 mg per kg per day IV is drug of choice in patients without AIDS. Blood urea nitrogen should be monitored and drug is discontinued if blood urea nitrogen reaches 40 mg/dl and resumed when it normalizes.

The addition of flucytosine (150 mg/kg per day) with amphotericin B (0.3 to 0.5 mg/kg per day) has fewer incidences of failures or relapses. Added benefits with combination are more rapid CSF sterilization and less nephrotoxicity. The course of therapy is for at least 6 weeks and

sometimes longer if CSF cultures for organism remains positive. This combination regimen has a Cryptococcal meningoencephalitis cure rate of 75 to 85% in immunocompetent patients and is less effective in patients with AIDS. Fluconazole (up to 400 mg daily orally) or itraconazole (up to 200 mg/day orally) are substitutes to flucytosine in AIDS patients and are quite more effective to prevent relapse when taken indefinitely[51]. Mortality is about 40% from Cryptococcal Meningoencephalitis independent of AIDS or other diseases.

Aseptic meningitis:

The most common cause of aseptic meningitis is viral infection. Other causes are carcinomatous meningitis and drug induced hypersensitivity reactions.

Etiology

The most important viruses are enteroviruses (coxsackie viruses, echoviruses, and human enteroviruses 68-71) make up to 80% of cases. Other viruses responsible for disease are mumps, herpes simplex virus-2, lymphocytic choriomeningitis, adenovirus, arthropod borne viruses, and HIV etc[52].

Causes of chronic and recurrent aseptic meningitis:

Infectious causes

- Tuberculosis and atypical mycobacterial.
- Fungal infections like (Cryptococcal, coccidian, histoplasmosis, blastomyces).
- Nocardia
- HIV
- Herpes type 2 (known as recurrent Mollaret meningitis).
- Lyme disease
- Syphilis
- Brucellosis
- Epidural abscess or hematoma
- Incompletely treated bacterial meningitis

Granulomatous and vasculitis causes

- Sarcoidosis
- Wegener granulomatosis

- Behcet's disease
- Vasculitis

Neoplastic causes

- Carcinomatous
- Lymphomatous

Chemical causes

- Leakage from cerebral or spinal epidermoid tumor, dermoid cyst, craniopharyngioma, or teratoma
- Instillation of irritative substances by lumbar puncture, spinal anesthesia or surgery.

Idiopathic

- Vogt-Kayanagi-Harada disease
- No cause determined in one-third of cases

Diagnosis

Clinical syndrome of aseptic meningitis consists of fever, headache, and signs of meningeal irritation along with lymphocytic pleocytosis in cerebrospinal fluid analysis.

Varying degrees of lethargy, irritability, and drowsiness may occur. Confusion, stupor, and coma are seen in case of encephalitis rather than meningitis. Photophobia and pain on movement of the eyes (ophthalmoplegia) are common associated features.

Rigidity of the neck and spine on forward bending points to presence of meningeal irritation (meningismus), but at first it is often unnoticed. In this clinical syndrome the Kernig sign and Brudzinski sign are often absent in the presence of manifest viral meningitis.

Other symptoms and signs of systemic effects of the invading virus may be present. These include sore throat, nausea and vomiting, easy fatigability, pain in the back and neck, cough, conjunctivitis, vomiting, diarrhoea, rash, adenopathy, etc.

The typical CSF profile is a lymphocytic pleocytosis as it is seen with other lymphocytic (tuberculosis), with normal glucose concentration, normal or mildly elevated protein level[53].

As a rule glucose content of cerebrospinal fluid is normal in case of aseptic meningitis. Therefore CSF picture showing low glucose concentration in conjunction with a lymphocytic or mononuclear pleocytosis points to tuberculous or fungal aetiology of meningitis or certain non-infectious disorder (sarcoid, neoplastic) meningitis.

Treatment

Acyclovir may be used in HSV-1 AND 2, EBV, VZV infection and HAART in HIV meningitis. But viral meningitis is usually self-limiting illness. Symptomatic care, like relief of headache, bed rest, adequate nutrition and maintaining fluid and electrolyte balance form the mainstay of therapy.

CSF CORTISOL and its role in meningitis:

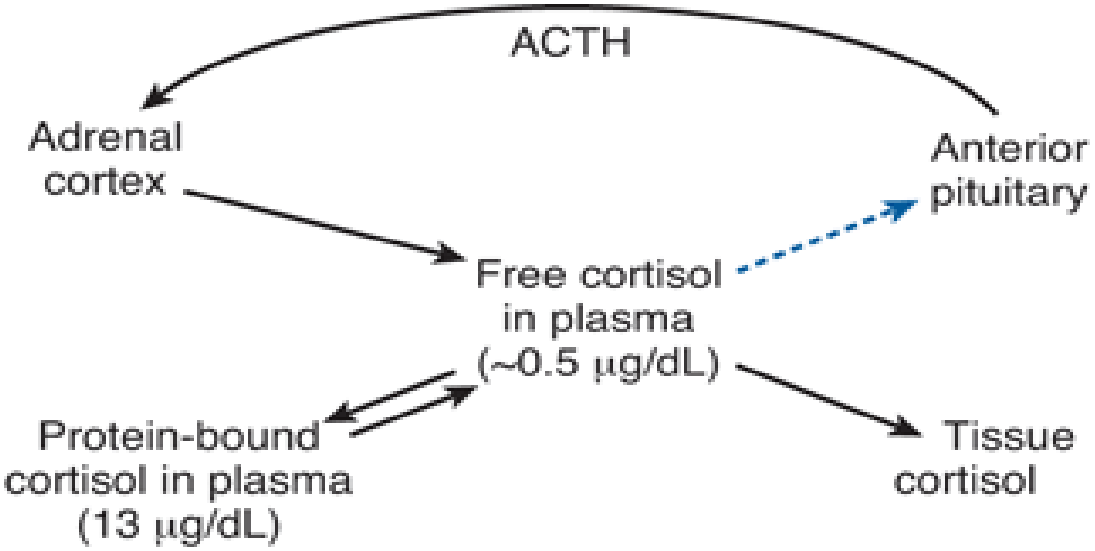
Cortisol is the main corticosteroid circulating in humans. Corticosteroids are synthesized in adrenal cortex from cholesterol.

The physiological actions of cortisol are:

- Maintaining electrolyte and water balance
- Regulation of carbohydrate metabolism (gluconeogenesis)
- Maintenance of vascular response to catecholamines.
- Anti-inflammatory activity and suppression of immune response.

Cortisol secretion is dependent on the integrity of the hypothalamic-pituitary-adrenal (HPA) axis and the steroid exerts a negative feedback on its own synthesis through this axis. Cortisol measurement is thus an important parameter in the investigation of apparent HPA dysfunction.

This picture shows interrelationship of free and bound cortisol



Cortisol is bound in the circulation to alpha gloubulin called transcortin or corticosteroid binding globulin. The half-life of cortisol in the circulation is longer (about 60-90 minutes), with approximately 1% excreted unchanged in the urine. This excreted fraction is called urinary "free cortisol" and if renal function is normal, will reflect the level of circulating non-protein bound cortisol. Most immunological methods employed for the determination of urinary free cortisol omit chromatographic steps thereby co-measuring cortisol metabolites. After metabolic breakdown, mainly in the liver, cortisol is excreted into the urine as dihydrocortisol and tetrahydrocortisol derivatives conjugated to glucuronicacid[44].

The circulating cortisol concentration is normally subject to a circadian rhythm, with the maximum level being reached in morning at 8-9 a.m. and the minimum around midnight(12am)[55].

Cortisol is the major glucocorticoid in humans, maintaining the stress reaction of the body to all kinds of physical and psychological discomfort. Increase in cortisol secretion can take place very quickly, within minutes in acute stress conditions, and can stay at high levels for long periods, sometimes days, months, and even years in chronic disease conditions[56].

Michal Holub et al have shown that CSF cortisol levels in patients with bacterial meningitis are highly elevated and correlate with disease severity[4].

The mechanism behind increased CSF cortisol in bacterial meningitis is associated with systemic inflammation, intense stress response and compromised blood brain barrier.

During critical illness, cortisol-binding globulin and albumin blood levels decrease by about 50%, leading to an increase in biologically active free cortisol.

It was suggested that balance between CSF cortisol and blood cortisol levels are controlled by active efflux of the hormone from the

brain. Perturbation of this mechanism by inflammation, together with reduced ability of brain cells to metabolize sterol molecules, may lead to persistent increase in CSF cortisol[4].

MATERIALS AND METHODS

Design: Cross sectional observational study in patients of suspected meningitis during August 2013 to July 2014.

Sample Size: 50 Patients which includes 40 study patients and 10 control subjects.

Case Definitions: Patients with clinical suspicion of meningitis presenting with fever, vomiting, altered sensorium and nuchal rigidity.

Inclusion Criteria

1. Age of patients more than 16 years

2. Patient with clinically suspected meningitis and confirm with lumbar puncture.

Exclusion Criteria

1. Partially treated cases with antibiotics before admission.

2. Patients treated with corticosteroids before admission.

3. Traumatic lumbar punctures for CSF collection.

Ten patients without any pre-existing neurological disorders will be included as controls.

All the patients were thoroughly examined clinically by preformed proforma and investigated as follows:

Working Indices:

Investigation

1. Hematological

    a) Complete haemogram.

2. Hepatic function tests

3. Renal function tests

4. Serum electrolytes

5. Random blood sugar: at the time of lumbar puncture

6. Chest X-ray PA view

7. Blood culture

8. CSF

    a) Cytochemical analysis including- cell count, cell type, protein, sugar

    b) CSF- CORTISOL estimation by chemiluminescent assay.

c) CSF- gram stain and Zeil Nelson stain

d) CSF- culture for mycobacteria and pyogenic organisms

e) CSF - TB PCR, HSV PCR, India ink, Cryptococcal Ag, ADA as and when required.

9. Serum cortisol.

Analysis of CSF:

A fresh sample of CSF collected in heparinised vial obtained by the lumbar puncture.

The different types of meningitis will be categorized as follows, according to cytochemical parameters[57].

1) Bacterial meningitis:

Protein: more than 45 mg /dl

White blood cells: 10/microliter to 10000 /microliter: neutrophil predominate

glucose: < 40mg/dl

CSF/ serum glucose: < 0.4

Cloudy or turbid appearance

Gram's stain and culture were done

2) Tubercular meningitis:

Protein: 0.1-0.5 g/L.

Cell counts: 10-500 cells/microL; lymphocytic pleocytosis.

Glucose: 20 - 40 mg/dl.

AFB and culture will be done.

3) Aseptic meningitis:

Protein: 20-80 mg/dl.

Glucose: normal to decrease.

Cell counts: 25-500 cells/microliter

Cell types: lymphocytic pleocytosis.

CSF CORTISOL Activity:

CSF-CORTISOL activity was estimated in all 40 cases by direct chemiluminescent assay and comparison was made among neutrophilic meningitis, lymphocytic meningitis, aseptic meningitis and controls.

Method: For in vitro diagnostic use in the quantitative determination of cortisol levels in CSF using the ADVIA Centaur CP system by direct chemiluminescent assay.

Principle: The ADVIA Centaur CP Cortisol assay is a competitive immunoassay using direct chemiluminescent technology. Cortisol in the patient sample competes with acridinium ester labeled cortisol in the Lite Reagent for binding to polyclonal rabbit anti-cortisol antibody in the Solid Phase. The polyclonal rabbit anti-cortisol antibody is bound to monoclonal mouse anti-rabbit antibody, which is covalently coupled to paramagnetic particles in the Solid Phase.

Specimen Collection and Handling:

The following recommendations for handling and storing CSF samples are furnished by the Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS):5

1. Universal precautions are taken for collecting all CSF samples.
2. Allow samples to clot adequately before centrifugation
3. Samples tubes are stoppered and always kept upright.
4. Do not use samples that have been stored at room temperature for longer than 8 hours.

5. The CSF are refrigerated at 2° to 8^{o} C if the assay is delayed and is not completed within 8 hours.

6. The CSF samples are freezed at or below -20°C in case sample is not assayed within 48 hours of collection.

7. Freeze samples only once and mix thoroughly after thawing.

   Before placing samples on the system ensure that samples have the following characteristics:

   A. Samples are free of fibrin or other particulate matter. If present remove particles by centrifugation.

   B. Samples are free of bubbles or foam.

Table- :Reagent preparation:

Reagent Pack	Reagent	Volume	Ingredients	Storage Stability
ADVIA Centaur COR ReadyPack primary reagent pack	Lite Reagent	2.5 mL/ Reagent Pack.	cortisol (~1.7 ng/mL) labeled with acridinium ester in buffered saline (~50 mg/mL), sodium azide (0.1%) and preservatives	2–8°C until the expiration date on the pack label
	Solid Phase	12.5 mL/ reagent Pack	rabbit anti-cortisol antibody (~1.1 ⌈g/mL) bound to monoclonal mouse anti-rabbit IgG antibody (~56 ⌈g/mL) covalently coupled to paramagnetic particles in buffered saline with sodium azide (0.1%) and preservatives.	2–8°C until the expiration date on the pack label

Loading Reagents:

Ensure that the system has sufficient primary and ancillary reagent packs.

Mix all primary reagent packs by hand before loading them onto the system. Visually inspect the bottom of the reagent pack to ensure that all particles are dispersed and suspended. Load the primary reagent packs in the primary reagent area. You can use the arrows on the end label as a placement guide. However, left, center, and right placement of the primary reagent packs is not required, because the ADVIA Centaur CP System has only one reagent probe. The system automatically mixes the primary reagent packs to maintain homogeneous suspension of the reagents.

Test Procedure

The system automatically performs the following steps:

1. Dispenses 20 microliter of sample into a cuvette.

2. Dispenses 50 microliter of Lite Reagent and 250 microL of Solid Phase and incubates for 9 .66 minutes at37°C.

3. Separates, aspirates, and washes the cuvettes with Wash 1.

4. Dispenses 300 microliters each of Acid Reagent (R1) and Base Reagent (R2) to initiate the chemiluminescent reaction.

5. Reports results according to the selected option, as described in the system operating instructions.

Table- Reference Values for CSF-CORTISOL:

NORMAL	< 2 microgram/dl
NONBACTERIAL	2-10 microgram/dl
BACTERIAL	>10 microgram/dl

It is recommended that each laboratory establish its own normal range representing its patient population.

Study Design: Cross sectional observational study.

ETHICAL CLEARANCE:

Ethical clearance was obtained from the Institutional Ethical Committee.

Statistical Analysis:

The data will be tabulated and analyzed. The quantitative data will be summarized in excel sheet.

Mean, Median, Standard Deviation will be estimated, in order to know the association between CSF cortisol levels, cytochemical analysis and culture results.

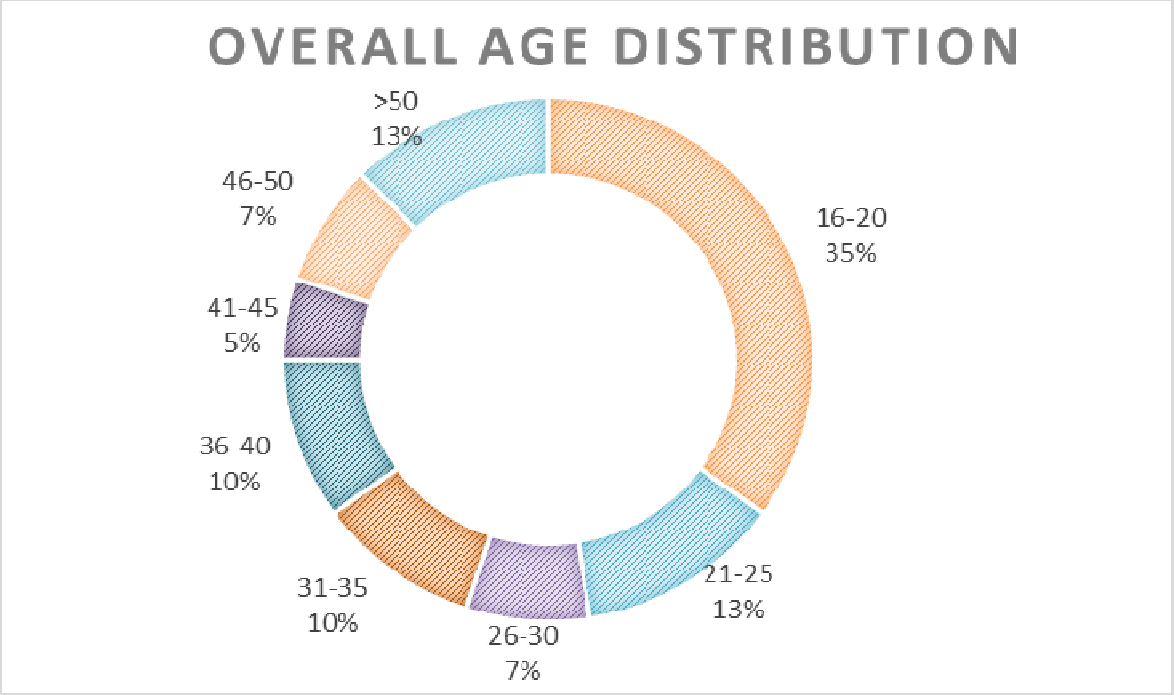
In all the tests “p” value less than 0.05 and 0.01 will be accepted as statistically significant and highly significant, respectively. SPSS16 software will be used. Microsoft word and excel will be used for preparation of graphs and charts.

Results

Table-1: Age-wise Distribution of cases

Age-wise Distribution	*Frequency*	*% distribution*
16-20	14	35%
21-25	5	13%
26-30	3	8%
31-35	4	10%
36-40	4	10%
41-45	2	5%
46-50	3	8%
>50	5	13%
Total	40	100%

Chart -1

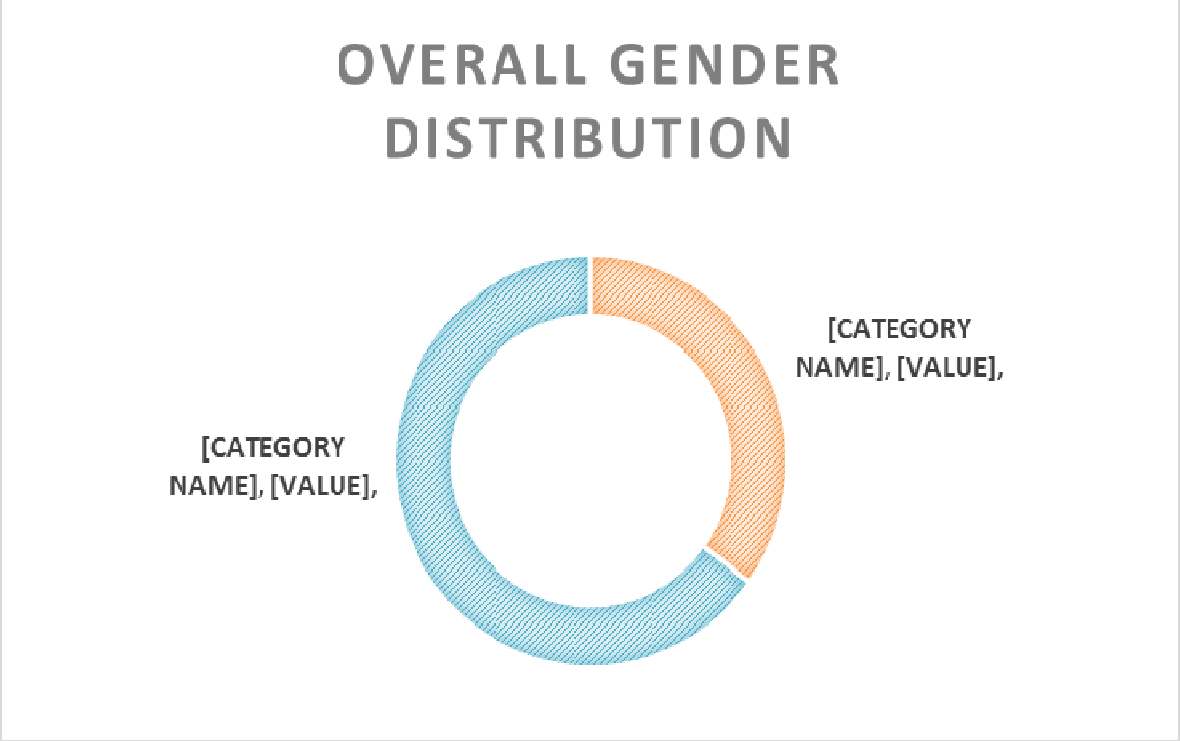


In our study the peak incidence of meningitis is seen in 16-20 years of age.

TABLE -2: Distribution among gender

Overall Gender Distribution		
Gender	**No of Cases**	**Percentage**
Female	14	35%
Male	26	65%
Total	40	100%

Chart-2:

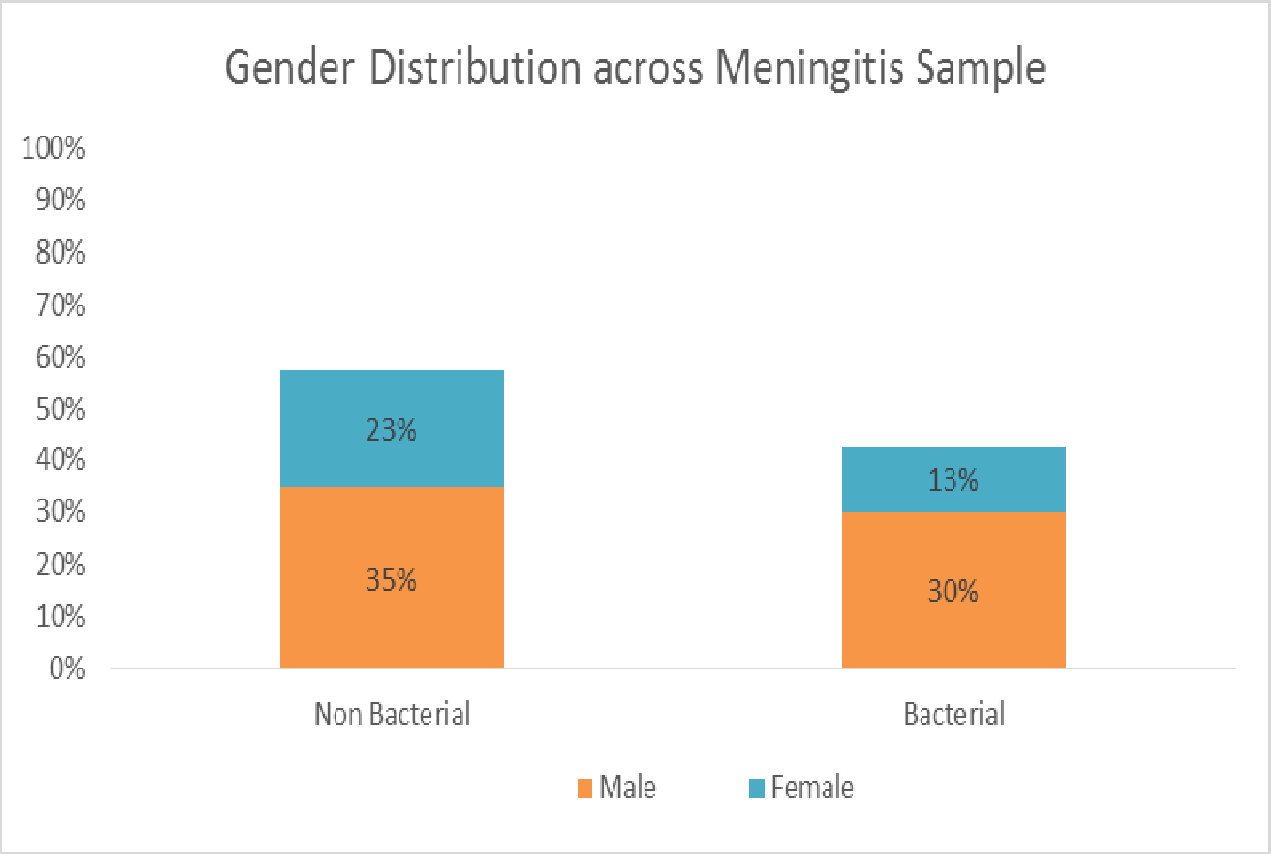


In the present study male were 65% and female cases were35%. Male to female ratio is 1.85:1

Table -3: Gender distribution across overall meningitis in sample

	Gender %		
Meningitis Diagnosis	**Male**	**Female**	**Total**
Non Bacterial	35%	23%	58%
Bacterial	30%	13%	43%
Total	65%	35%	100%

Chart -3:



In our study, in 65% were male patients and 35% were female patients suffering from meningitis. Out of this, 23% and 35% for non-bacterial meningitis respectively.in case of bacterial, male: female incidence was 30% and 13% respectively.

Table- 4: Gender Distribution across Meningitis in the sample:

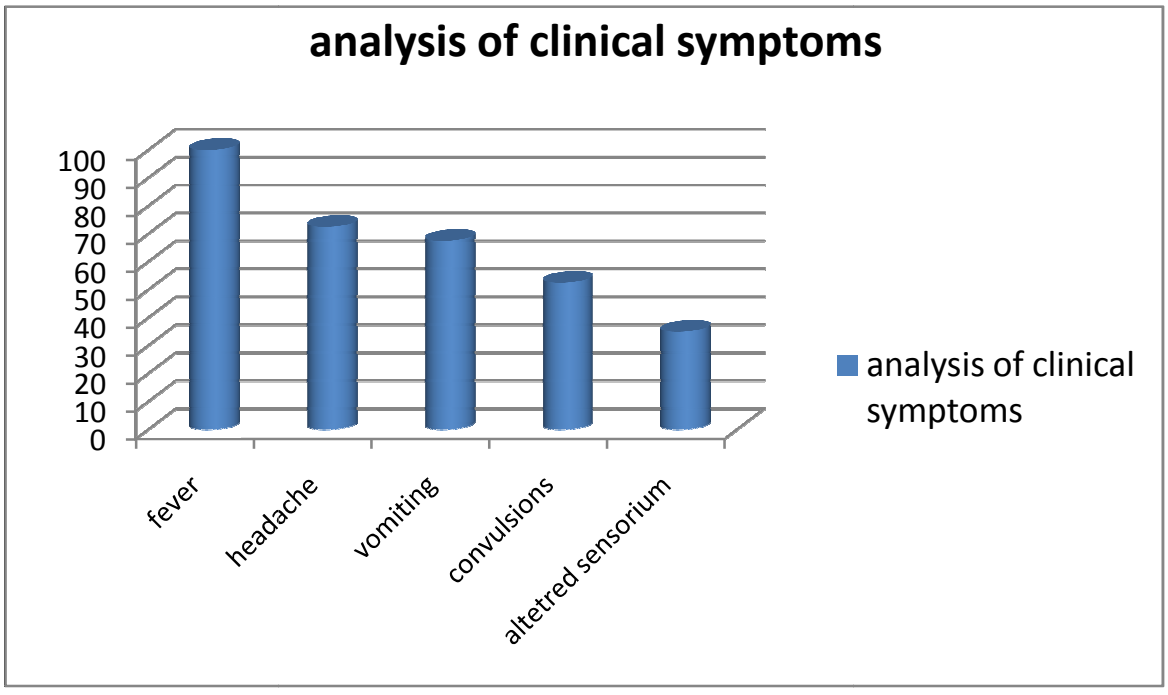
	Gender		
Meningitis Diagnosis	**Male**	**Female**	**Total**
Neutrophilic	12	5	**17**
Lymphocytic	9	7	**16**
Aseptic	5	2	**7**
Total	26	14	40

In our studies out of 40 patients 17 cases had neutrophilic meningitis, 16 cases had lymphocytic meningitis and 7 cases had Aseptic meningitis.

Table 5- Analysis of clinical symptoms

Clinical symptoms	no of cases	percentage
Fever	40	100%
Headache	29	72.5%
Vomiting	27	67.5%
Altered sensorium	21	52.5%
Convulsions	14	35%

Chart-4



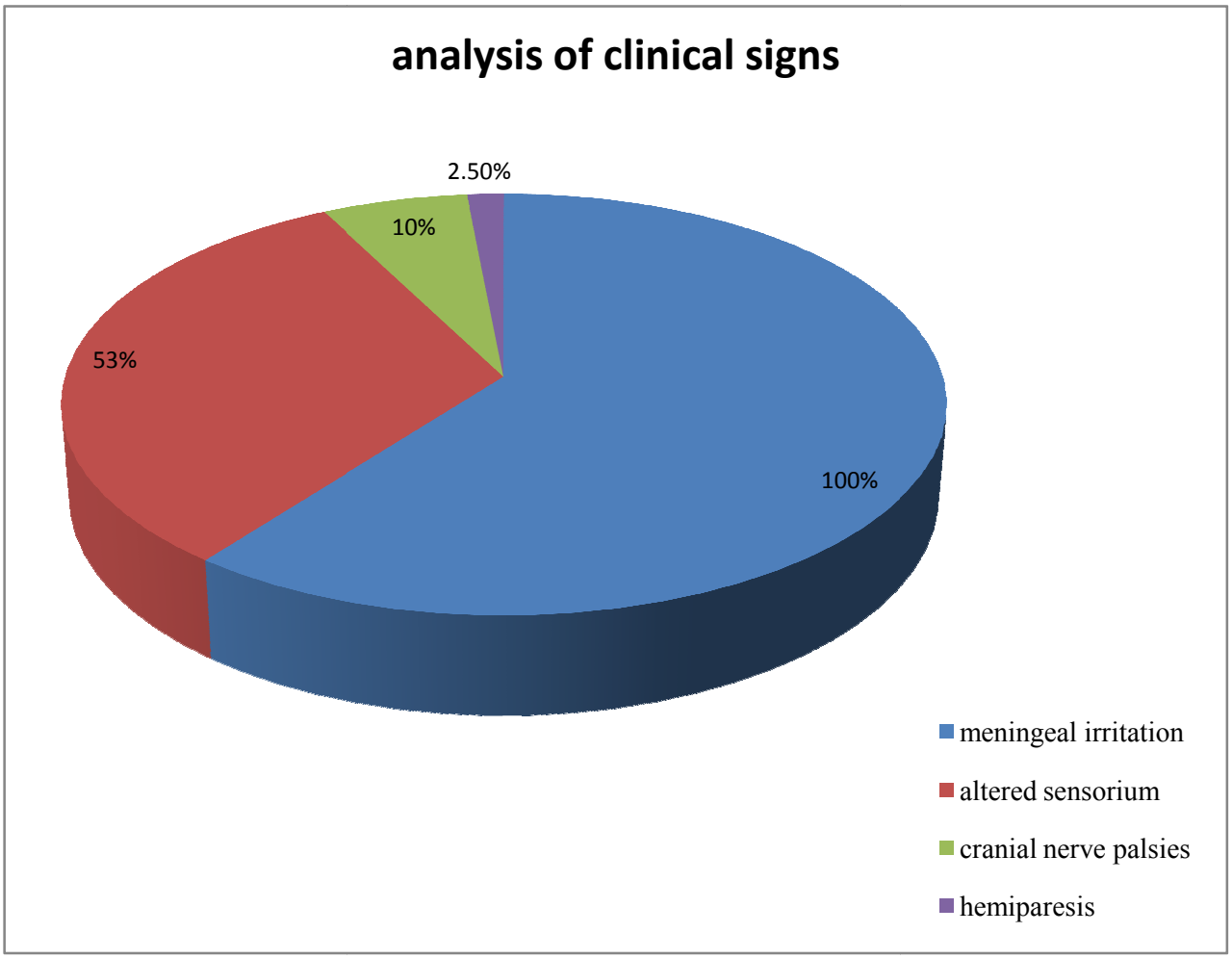
In our studies among 40 patients of meningitis, all patients had fever (100%).headache was present in 29 patients (72.5%), vomiting was seen in 27 patients (67.5%), various stages of altered sensorium is seen in 21 patients (52.5%), convulsions in 14 cases (35%).

Table6: Analysis of clinical signs

Signs	No. of cases	Percentage
Signs of meningeal irritation	40	100%
Altered sensorium	21	53%
Drowsiness	15	37.85%
Irritability	4	10.09%
Stupor	2	5.04%
Coma	0	0
Cranial nerve involvement	4	10%
6^{th} nerve palsy	3	7.5%
7^{th} nerve palsy	1	2.5%
Motor system involvement		
Hemiparesis	1	2.5%

Among the 40 cases of meningitis, signs of meningeal irritation were seen in all (100%) of cases. Altered sensorium was seen in 21 cases (53%). Cranial nerve palsies were present in 4 cases, 3 were 6^{th} nerve palsy and 1 was facial nerve palsy.

Chart:5

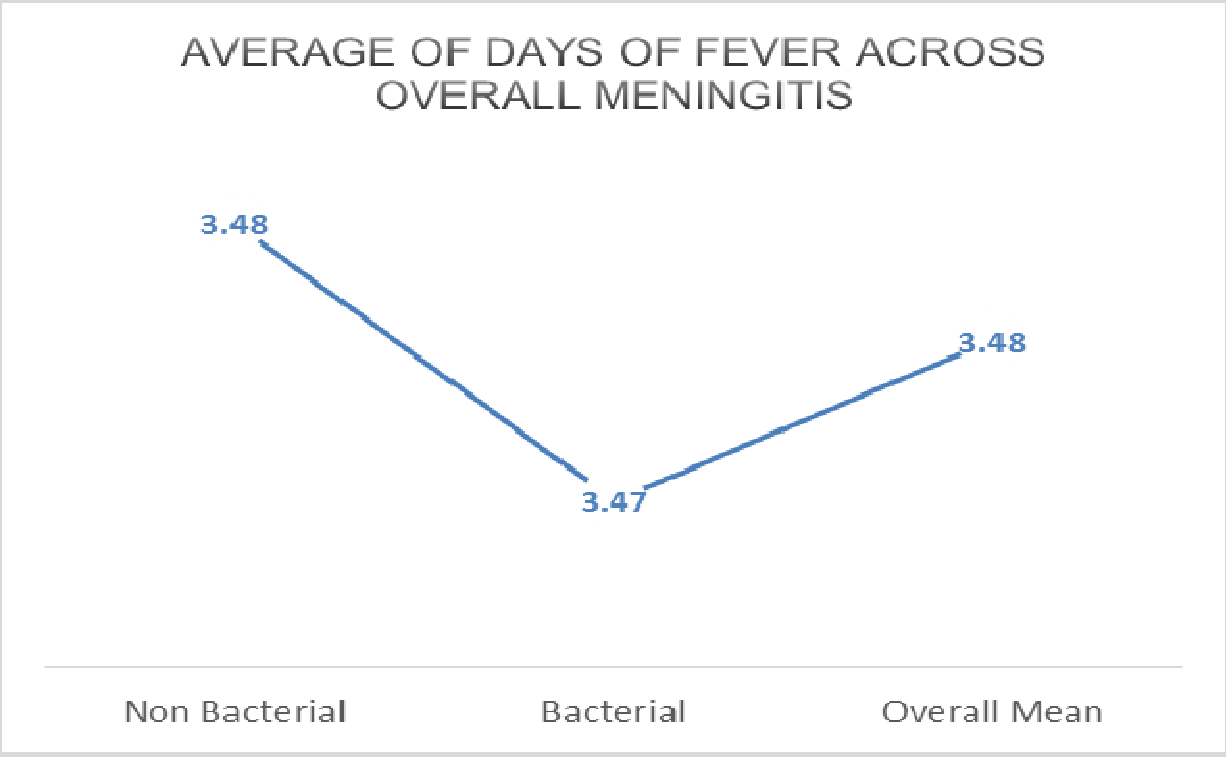

analysis of clinical signs
2.50%
10%
53%
100%
meningeal irritation
altered sensorium
cranial nerve palsies
hemiparesis

Analysis of Individual Clinical Symptoms

Table-7: Average of days of fever across overall meningitis

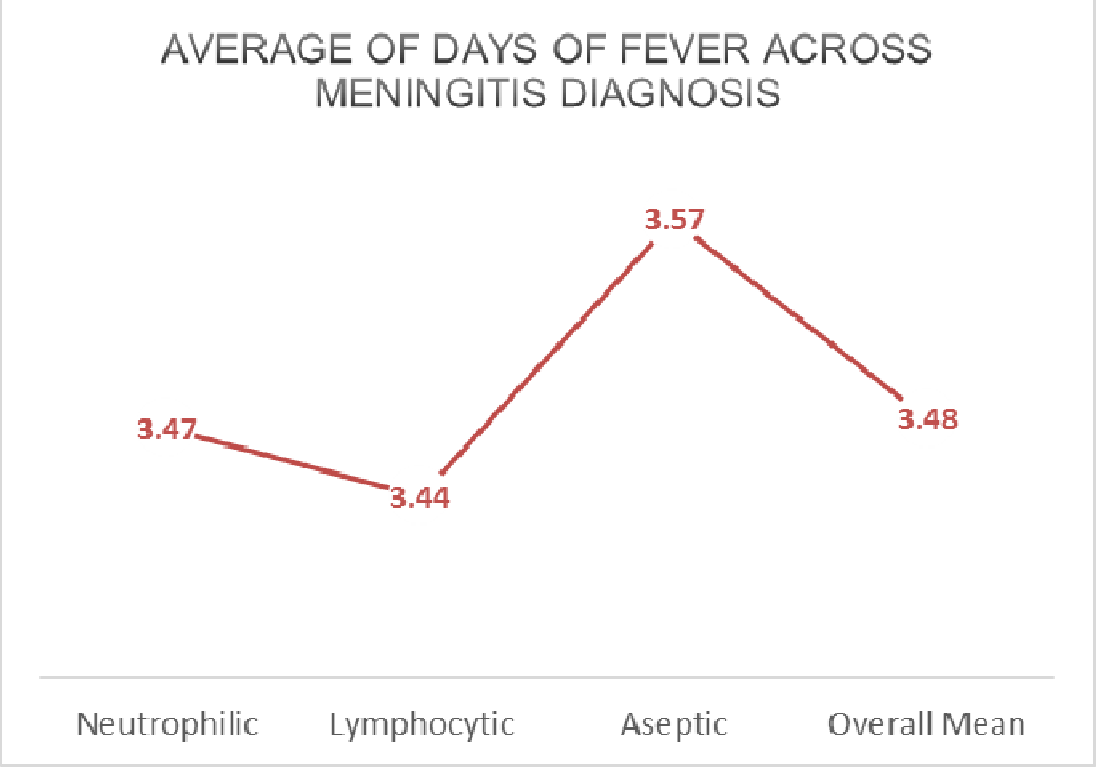
Overall Meningitis	Mean
Non Bacterial	3.48
Bacterial	3.47
Overall Mean	3.48

Chart-6:



In the present study there was no significant correlation between the total of days of fever in bacterial and nonbacterial meningitis.

Chart-7: Average of Days of Fever across Neutrophilic, Lymphocytic, Aseptic meningitis

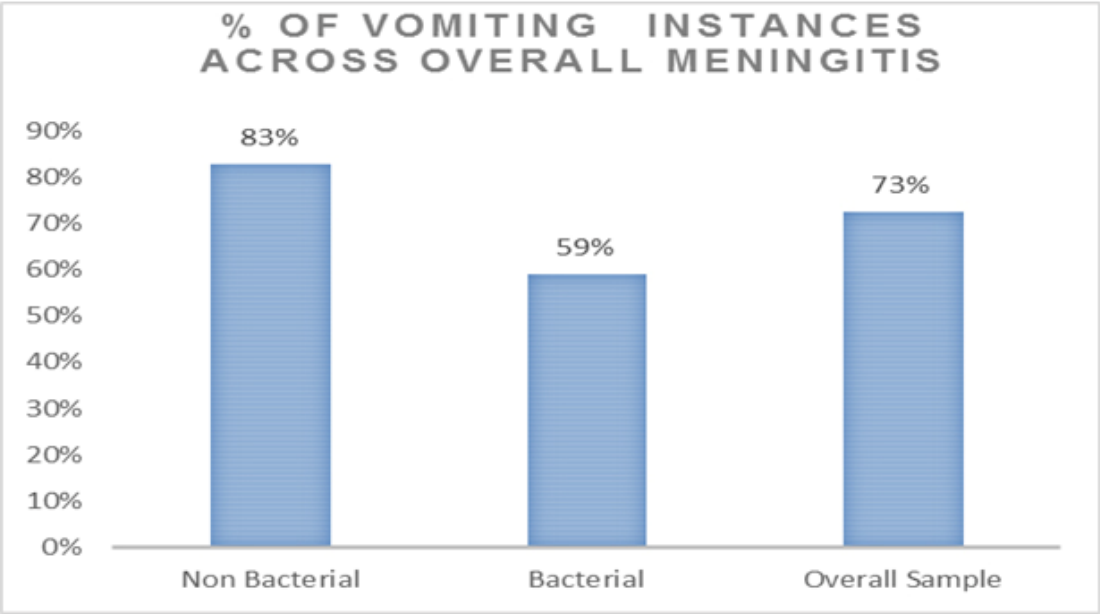


In the study there was no correlation between the days of fever and neutrophilic, lymphocytic and aseptic meningitis.

Table-8: Distribution of Vomiting Instances across Overall Meningitis Diagnosis

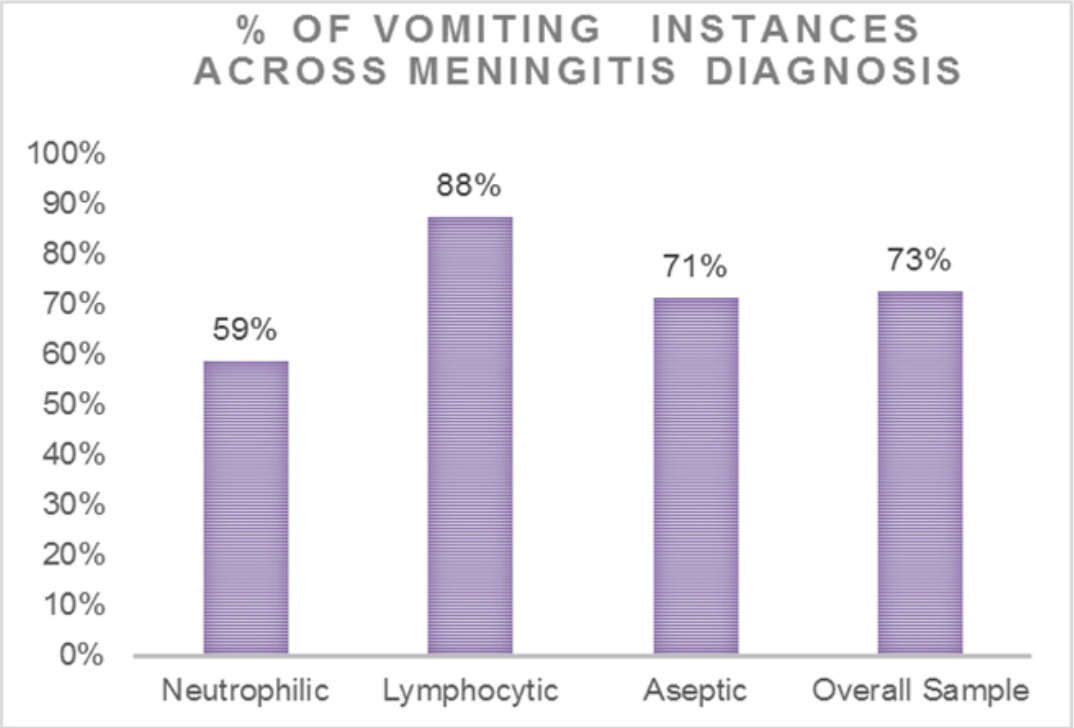
Overall Meningitis Diagnosis	%
Non Bacterial	83%
Bacterial	59%
Overall Sample	73%

Chart-8: % of Vomiting Instances across Overall Meningitis Diagnosis



In our study, among the 40 meningitis patients 59% of bacterial meningitis had vomiting and 89 % of nonbacterial had vomiting.

Chart-9: Distribution of Vomiting Instances across Neutrophilic, Lymphocytic, Aseptic meningitis

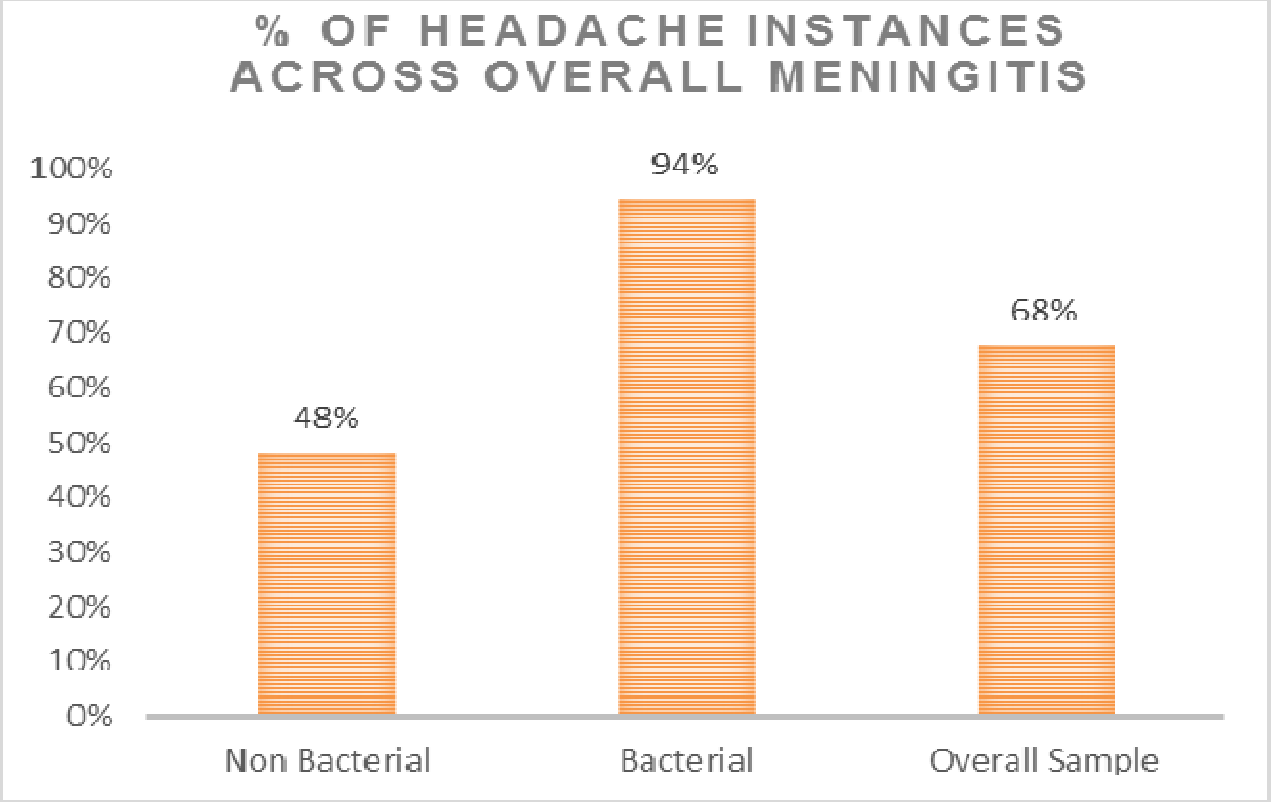


In our present study incidence of vomiting was more among lymphocytic meningitis (88%) compared to neutrophilic (59%) meningitis and aseptic (71%) meningitis.

Table-9: **Distribution of headache instances across overall meningitis**

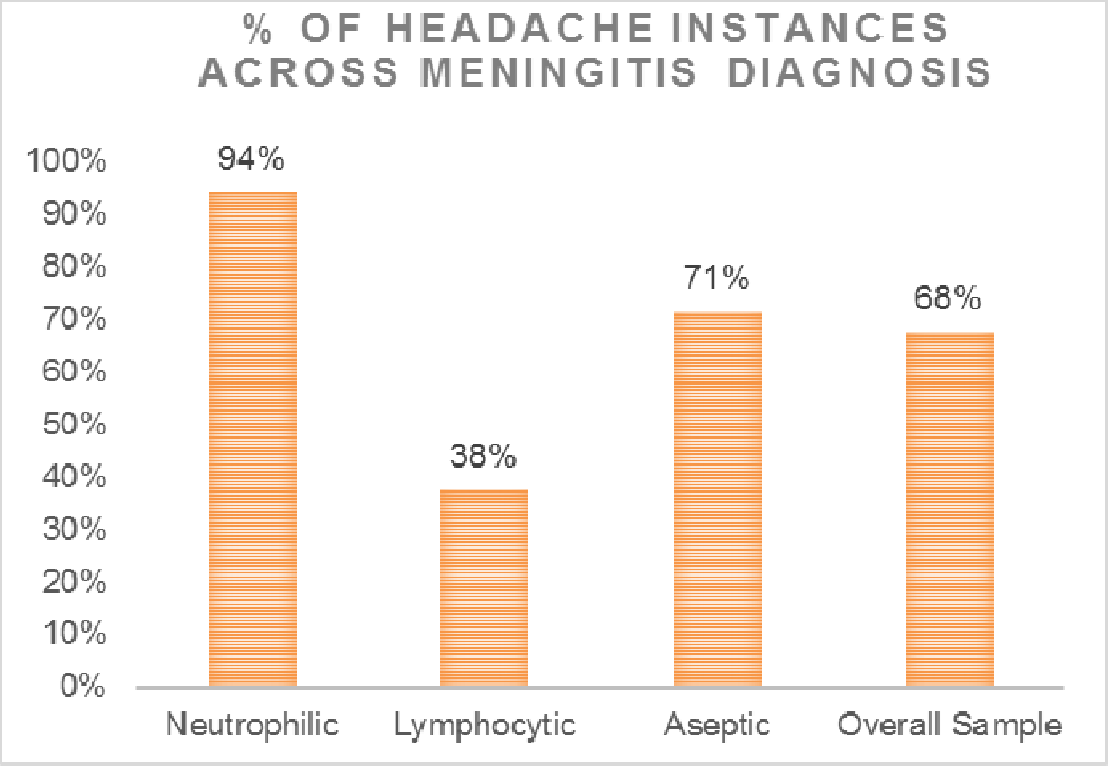
Overall Meningitis	%
Non Bacterial	48%
Bacterial	94%
Overall Sample	68%

Chart-10:



In the study percentage incidence of headache was more among bacterial (94%) than nonbacterial (48%) meningitis.

Chart-11:

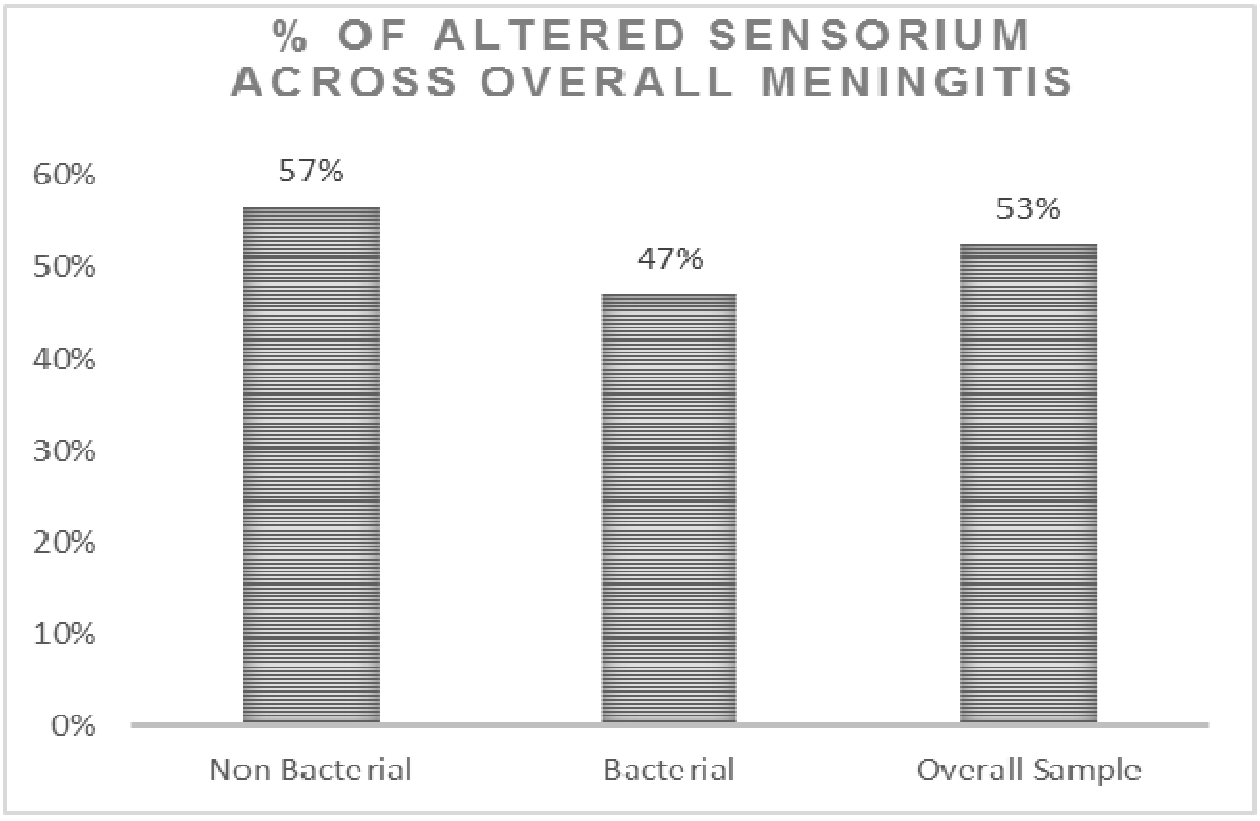


In the study headache was common was present in 94% of neutrophilic meningitis.In case of lymphocytic meningitis and aseptic meningitis the headache was present in 38% and 71 % patients respectively.

Table-10:Distribution of ALTERED SENSORIUM Instances across Overall Meningitis

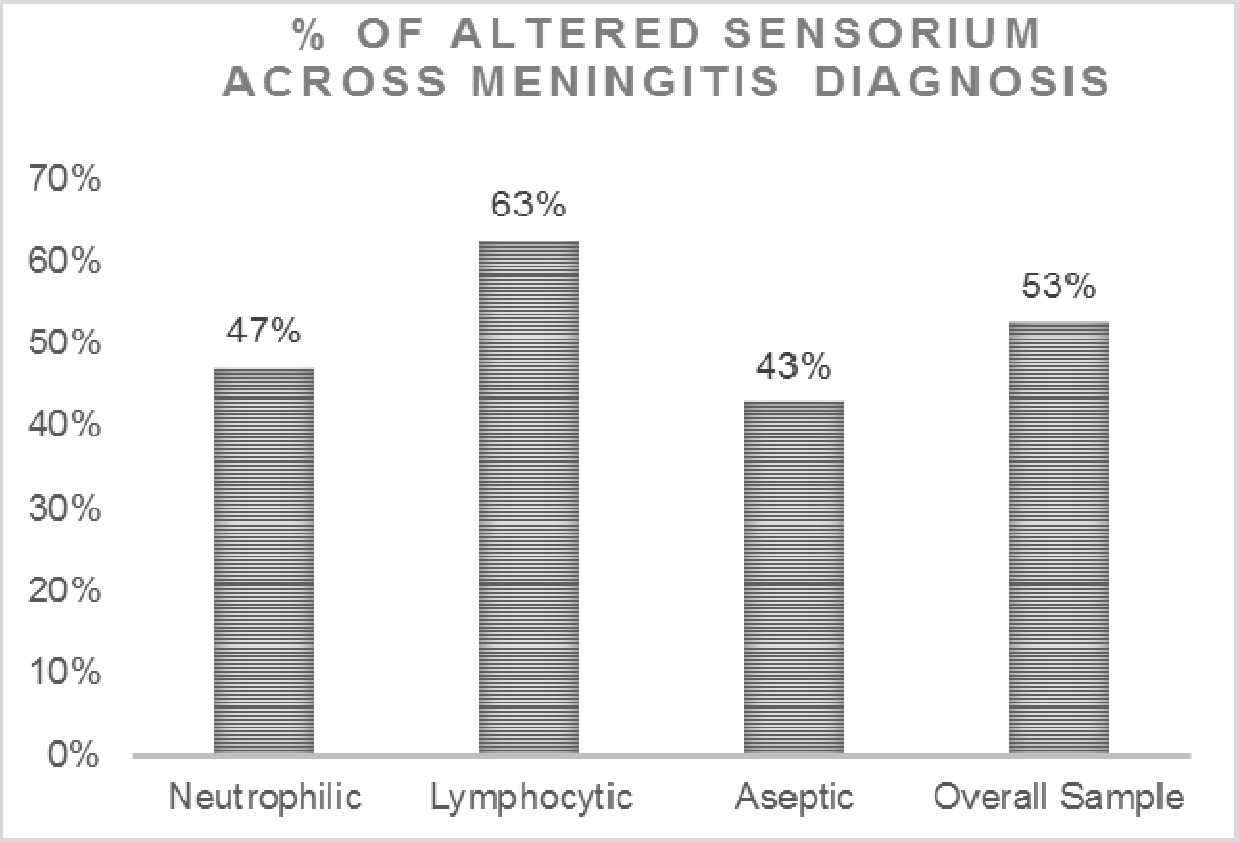
Overall Meningitis	%
Non Bacterial	57%
Bacterial	47%
Overall Sample	53%

Chart-12:



Over incidence of altered sensorium was 53%. Nonbacterial meningitis (57%) incidence was more in comparison with no bacterial (47%) meningitis.

Chart-13



The presence of altered sensorium was more in Lymphocytic meningitis (63%) compared to neutrophilic meningitis and aseptic meningitis in the present study.

Table-11: Distribution of Instances of Seizure across Overall Meningitis

	PERCENTAGE		
% of Instances of SEIZURES	**Non Bacterial**	**Bacterial**	**Total**
0	70%	59%	65%
1	22%	6%	15%
2	4%	29%	15%
3	0%	6%	3%
6	4%	0%	3%
Total	100%	100%	100%

In our study, 30% of non-bacterial meningitis and 41% of bacterial meningitis had seizures.

Chart-14

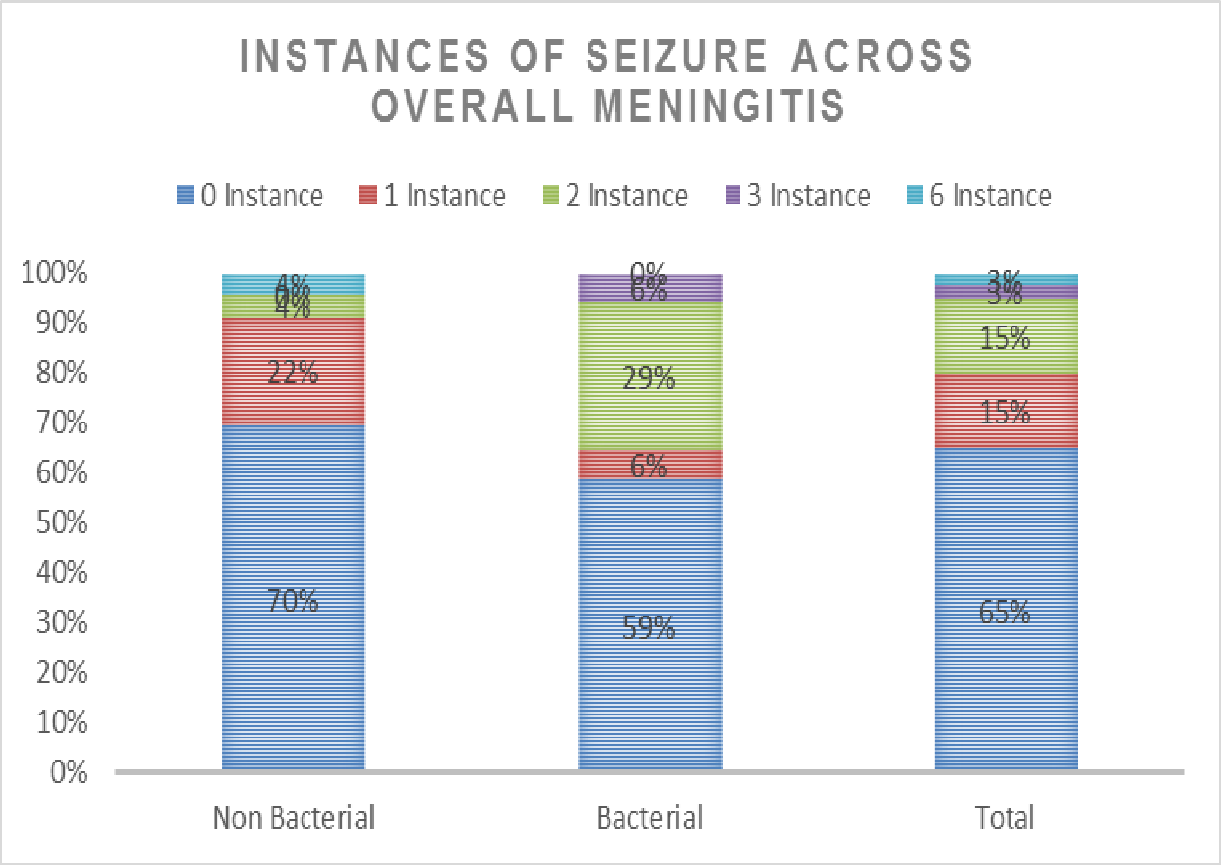
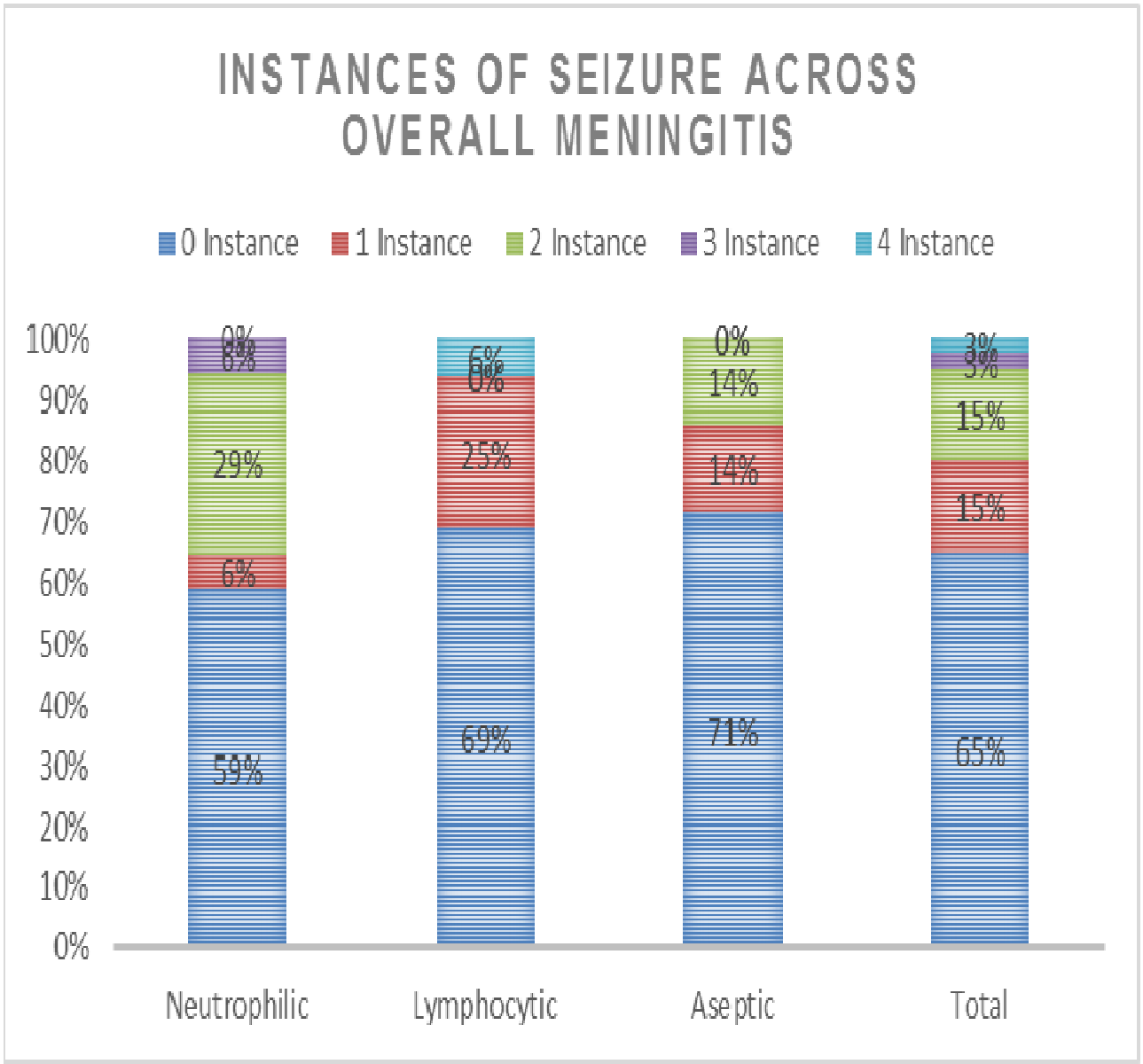

INSTANCES OF SEIZURE ACROSS OVERALL MENINGITIS
0 Instance
1 Instance
2 Instance
3 Instance
6 Instance
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
4%
4%
22%
70%
6%
29%
6%
59%
3%
15%
15%
65%
Non Bacterial
Bacterial
Total

Chart-15:



Furthermore 22% of non-bacterial and 6% bacterial had one episode of seizure respectively. 35% of bacterial meningitis group had more than one episode of seizure as compared to non-bacterial meningitis group (8%).

Table12: Cytological and bio chemical parameters of blood and CSF in different group of meningitis patients

Parameters	Normal ranges	Neutrophilic meningitis	Lymphocytic meningitis	Aseptic meningitis
Blood				
WBC count(cells/mm^3)	4000-11000	14900 (11824-18635)	7350 (4160-10118)	6950 (3630-7950)
CSF				
Cell count(cells/mm^3)	<5	210 (90-400)	182 (85-300)	32 (20-40)
Cell type (predominant)	Usually lymphocytes	Neutrophils	Lymphocytes	Lymphocytes
Protein (mg/dl)	20-45 mg/dl	120 (80-165)	119 (90-160)	39 (30-50)
Glucose (mg/dl)	>2/3 of blood glucose	40 (26-69)	42 (26-86)	74 (60-82)
CSF/Serum glucose ratio	>0.6	0.28 (0.288-0.34)	0.3 (0.28-0.42)	0.64 (0.62-0.66)

In the present study among 40 meningitis cases, the WBC count in neutrophilic meningitis is high compared to lymphocytic meningitis and aseptic meningitis. Among the neutrophilic meningitis cases mean CSF cell count is 210cells/mm^3, mean protein level is 120 mg/dl, mean CSF glucose is 40 mg/dl and mean CSF/Serum glucose ratio is 0.28.

Table -13: Average of Protein, Sugar and RBS across Neutrophilic, Lymphocytic, Aseptic meningitis

Meningitis Diagnosis	PROTIEN	SUGAR	RBS
Neutrophilic	119.94	40.00	140.76
Lymphocytic	119.56	42.81	140.13
Aseptic	39.29	74.00	118.57
Overall Sample	105.68	47.08	136.63

In the present study neutrophilic and lymphocytic meningitis mean protein was 119.94mg/dl and 119.56mg/dl respectively. There was significant difference when compared with aseptic meningitis. Similarly the CSF glucose was low in neutrophilic and lymphocytic meningitis (≈40mg/dl) in comparison with aseptic meningitis (74mg/dl).

Chart-16:

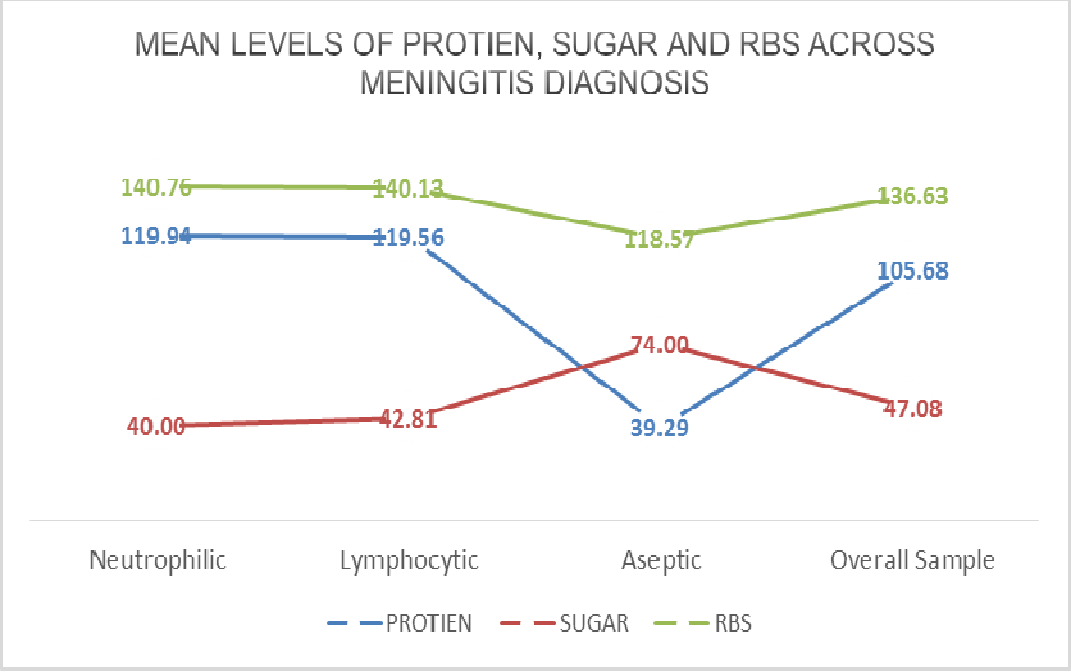


Table-14: CSF Cortisol Level across Meningitis Diagnosis

Overall Meningitis Diagnosis	Statistics	CSF Cortisol Levels
Non Bacterial	Mean	3.8
	Median	4.0
	Maximum	5.0
	Minimum	2.0
	No of Cases	23
Bacterial	Mean	13.1
	Median	14.0
	Maximum	17.0
	Minimum	4.0
	No of Cases	17
Total	Mean	7.7
	Median	5.0
	Maximum	17.0
	Minimum	2.0
	No of Cases	40.0

Mean CSF cortisol level in bacterial meningitis (13.1µg/dl) group was significantly higher as compared to non-bacterial meningitis (3.8µg/dl) and control group (1.05µg/dl).

Chart-17:CSF Cortisol Level across Meningitis Diagnosis

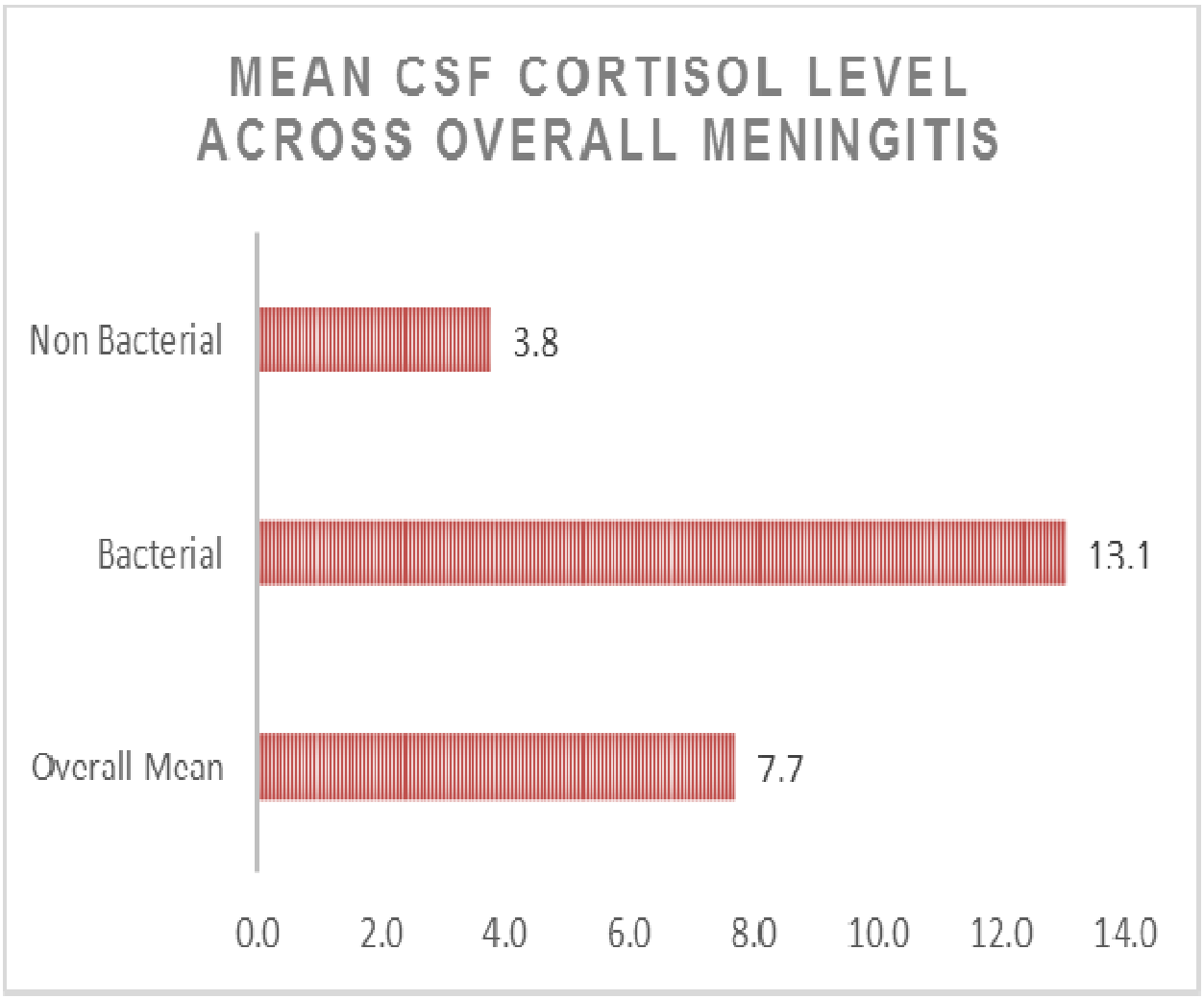


Table-15: CSF cortisol level across neutrophilic, lymphocytic, aseptic meningitis.

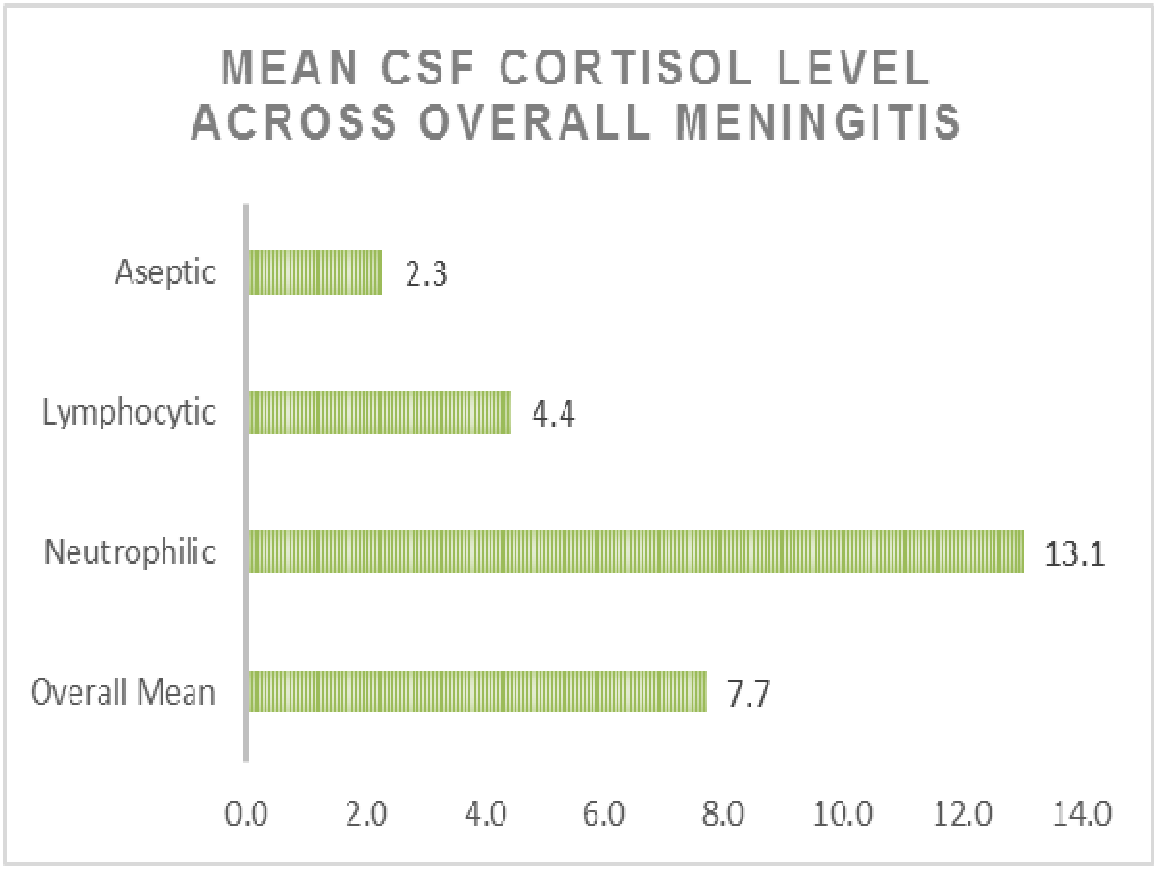
Meningitis Diagnosis	Statistics	CSF Cortisol Levels(µg/dl)	F value	P value
Neutrophilic	Mean	13.06		
	Median	14		
	Maximum	17		
	Minimum	4		
	No of Cases	17		
Lymphocytic	Mean	4.44		
	Median	5		
	Maximum	5	110.721	0.000
	Minimum	3		
	No of Cases	16		
Aseptic	Mean	2.29		
	Median	2		
	Maximum	3		
	Minimum	2		
	No of Cases	7		
Controls	Mean	1.05		
	Maximum	1.7		
	Minimum	0.2		
	No of cases	10		

The P value indicates that the means are different.

Mean CSF cortisol level in neutrophilic meningitis was significantly high as compared with lymphocytic, aseptic meningitis and control group.

It is statistically significant with p value of 0.000.

Chart 18: CSF Cortisol levels across different group of meningitis



The mean CSF cortisol levels in neutrophilic meningitis are 13.1µg/dl, lymphocytic meningitis is4.4µg/dl and aseptic meningitis is 2.3µg/dl.

Table16- Comparison of CSF cortisol levels and neutrophilic, lymphocytic and aseptic meningitis

CSF Cortisol Levels. Tukey HSD						
			Mean Difference (I-J)	Std. Error	Sig. (P value)	95% Confidence Interval
					Lower Bound	Upper Bound
Neutrophilic	Lymphocytic	8.621*	0.688	0.000	6.94	10.3
	Aseptic	10.773*	0.887	0.000	8.61	12.94
Lymphocytic	Neutrophilic	-8.621*	0.688	0.000	-10.3	-6.94
	Aseptic	2.152	0.895	0.054	-0.03	4.34
Aseptic	Neutrophilic	-10.773*	0.887	0.000	-12.94	-8.61
	Lymphocytic	-2.152	0.895	0.054	-4.34	0.03

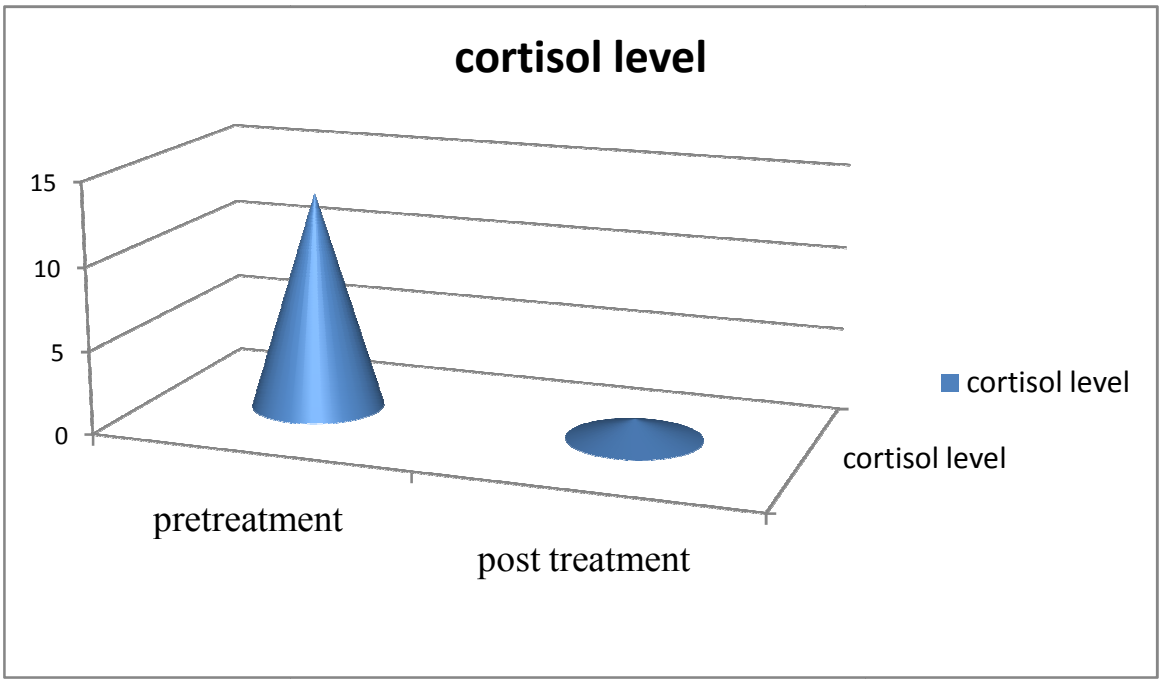
.*. The mean difference is significant at the 0.05 level

However the Tukey test confirm that average levels of CSF Cortisol is significantly higher for Neutrophilic when compared to Lymphocytic and Aseptic and that the average levels of CSF Cortisol is not significantly different between Lymphocytic and Aseptic meningitis.

Table17– CSF cortisol level in bacterial meningitis in relation to treatment

	Mean CSF CORTISOL levels (µg/dl)	
	Pre treatment	Post treatment
Bacterial meningitis	13.1	1.2

Chart -19:



In the present study there was significant reduction in CSF cortisol levels post treatment.

DISCUSSION

Forty cases were studied and the diagnostic utility of CSF cortisol was evaluated in differentiating neutrophilic meningitis and lymphocytic meningitis, aseptic meningitis. CSF samples from 10 subjects without any pre-existing neurological disorders who underwent spinal anesthesia were taken as controls.

The peak incidence of meningitis in the present study was seen in patients in the age group between 16-20 years. In the Michal Holub et al study, the mean age was 42 years [4]in the present study the incidence in males was 65% and in females was 35%. In Michal Holub et al study the incidence in males was 61.7% and in females was 38.3%[4].

In the present study, the most common symptom was fever (100%) followed by headache (72.5%) and vomiting (67.5 %.). In van de Seek D et al study, the classic triad of fever, Nuchal rigidity and change in mental status was present only in 44% of cases. However 95% had at least two of the four symptoms of headache, fever, neck stiffness and altered mental status[59]. In the present study, Seizures were noted in 36% and is comparable with Van de Beek et al study, the incidence of seizures was 17%[59]. In the present study, the signs of meningeal irritation were present in 100% of cases. Neck rigidity in 100% of cases, Kernig's in

35.5% of cases and Brudzinski's sign 8.7% of cases. In Khatua et al study, neck rigidity was noted in 54% case and Kernig's sign in 40% of cases[60].

In the present study, cranial nerve involvement was seen in 4 cases (10%), three sixth nerve palsy and one seventh nerve palsy which is less common compared to other studies done by Van de Beek et al(33%) . Virmani et al (27%) and Khatua et al (25%) [59,60]. In the present study, Motor deficit was seen in 1 case (5.71%) where as in Diederik Van de Beek et al study motor deficit was observed in 23% cases[59].

In the present study, mean CSF cortisol levels were significantly higher in neutrophilic meningitis (13.06µg/dl) as compared to lymphocytic meningitis (4.44 µg/dl), Aseptic meningitis (2.29 µg/dl) and controls (1.05 µg/dl). It is statistically significant, p value being 0.0001. Similarly, in Michal Holub et al study, the mean CSF Cortisol was significant elevated in neutrophilic meningitis; (133nmol/ l) compared to aseptic (17nmo/l) and controls (10nmol/l)[4], p value being highly significant (0.001). Beran et al study showed that the mean CSF cortisol was significantly elevated in aseptic meningitis compared to controls. In the present study, similar observations were made, mean CSF cortisol level in aseptic meningitis (2.29µg/dl) compared to controls (l.05µg/dl).

In the present study, it was observed that there was no significant difference in mean CSF cortisol levels in culture positive (l6.05) and culture negative (13.51) neutrophilic meningitis, p value being <0.069.Only 8 patients; of bacterial meningitis showed culture positive. The 8 cultures were positive and the organisms were streptococcus pneumoniae (7), Neisseria meningitidis (1) and hemophilus influenzae (1). In Michal Holub et al study, it was observed that there was significant difference in CSF cortisol levels in culture positive(162nmol/l) and culture negative percent(103nmol/l). Total number of patients with bacterial meningitis showing culture positive was thirty five (74%) out of these, 14 were caused by Neisseria meningitides (40%). 11 cases were due to streptococcus pneumonia (31%). Others included E.coli, Streptococcus hemolyticus, Staphylococcus aureus, and listeria monocytogenes, hemophilus influenza.

In the present study, a direct correlation was observed between mean CSF cortisol levels (13.06). It was statistically significant, p value being 0.000. In Michal Holub et al study similar observations were made, a direct correlation between mean CSF cortisol levels(133 nmol/l) and mean serum cortisol levels(939+/-534 nmol/l). That is as the CSF cortisol level raises, serum cortisol levels also raise. In Singhi SC et al study, free mean cortisol levels were significantly higher in bacterial meningitis compared to aseptic meningitis[4].

The mean CSF cortisol pre-treatment levels (13.06) showed significant reduction post treatment (1.2). Similar observations were made in Michal Holub et al study[4].

In the present study, altogether 28 patients (80%) were admitted to Intensive Care Unit, with a median length of stay in ICU being 7 days and median length of stay in hospital was 18 days. Favorable outcomes were observed in 25patients (85.7%). Three patients (8 .5%) succumbed and two patients (5.71%) exhibited neurological sequelae. In Michal Holub et al study, altogether 40 patients (85%) were admitted to Intensive Care Unit with a median length of stay of 8 days (4-l 5) days and median length of stay in hospital being 24 days. Favorable outcomes of bacterial meningitis were observed in 17 patients (77%) and 7 patients (l 5%) succumbed within 28 days after admission, 4 patients (8%) exhibited severe neurological sequelae.

CONCLUSION

1) CSF cortisol levels were significantly higher in bacterial meningitis group compared to non-bacterial meningitis group taking the cut off value of 10µg/dl.

2) CSF cortisol is significantly reduced following specific treatment in bacterial meningitis group. This can be a useful guide in monitoring the response to therapy.

SUMMARY

- Forty cases were studied and the diagnostic utility of CSF cortisol was evaluated in differentiating neutrophilic meningitis, lymphocytic meningitis, and aseptic meningitis. Ten subjects without any pre-existing neurological disorders who underwent spinal anaesthesia were taken as control.

- The peak incidence of present study was seen in patients in the age group between 16-20 years (35%).The mean age was 42.6 years.

- In the present study, the incidence in males was 65 %(26) and in females was 35 %(14).

- The most common symptom was fever (100%) followed by headache (72.5%) and vomiting (67.5%).

- The signs of meningeal irritation were present in 100% of cases. Seizures were noted in 36% of case. Cranial nerve involvement was seen in 4 cases (10%). Motor deficit was seen in 1 case (2.5%).

- Mean CSF cortisol levels were significantly higher in neutrophilic meningitis (13.06µg/dl) as compared to lymphocytic meningitis (4.44µg/dl), Aseptic meningitis (2.29µg/dl) and controls (l .05µg/dl).

- The CSF cortisol in bacterial meningitis pre-treatment levels showed significant reduction post treatment which was 1.2µg/dl.

- CORTISOL activity in CSF is a rapid, relatively inexpensive and simple procedure can be of great value as a diagnostic marker in the early diagnosis of Bacterial meningitis and Nonbacterial meningitis, helping in early institution of appropriate treatment and thereby decreasing mortality and complications.

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PROFORMA

Name: Age: I.P.No:
Occupation: Sex:
Address: Date of admission:
DIAGNOSIS:

History of Present Illness

1 Mode of onset: Sudden/Gradual, Low/High Grade

2. Fever
- Continuous/remittent/intermittent
- Associated with Chills & Rigors
- Diurnal Variation
- Night sweats

3Headache:
- Continuous /Paroxysmal
- Mild/ Moderate/ Severe
- Localization of Pain
- Aggravating Factors
- Relieving Factors
- Diurnal Variation
- A/W Visual Disturbances/ Vomiting

4. Altered Sensorium:
- Mental Confusion
- Altered consciousness
- Delirium

5. Convulsions:
- Frequency
- Generalised /Focal
- Tongue Bite
- Sphincter control
- Loss of consciousness

6. Vomiting:
- Numbs of times
- Quantity
- Nature
- Projectile

7. Paralysis Weakness:

Monoplegia
Hemiplegia
Paraplegia
Quadriplegia

8. Speech:

Loss of Speech
Dysarthria

9 Cranial Nerves:

Loss of smell
Defective Vision
Diplopia
Squint
Difficulty in mastication
Deviation of angle of month
Vertigo
Tinnitus
Deafness
Nasal Regurgitation
Dysphagia
Choking

10. Loss of Appetite.& Loss of Weight
11. Diabetes

12. Hypertension

Past history

Tuberculosis

Pulmonary/Pleural
Lymphadenitis
Tuberculosis of GIT
Tuberculosis of Bones& Joints

Family history tuberculosis

Personal history:

1. Smoking
2. Alcoholism
3. Diet
4. Marital status
5. Number of Children

PHYSICAL EXAMINATION

1. Built
2. Nourishment
3. Anaemia
4. Jaundice
5. Cyanosis
6. Clubbing
7. Significant lymphadenopathy
8. Stigmata of tuberculosis
9. Vital signs:

Pulse rate
BP
RR
Temperature

CNS EXAMINATION

Higher functions:

1. Level consciousness
2. Appearance & Behaviour
3. Hallucinations and delusions
4. Orientation to time, place, person
5. Memory & Intelligence
6. Speech

Examination n of cranial nerves:

1. Olfactory: Anosmia/ Parosmia
2. Optic: Visual Acuity
   Field of vision
   Vision
   Fundus
3. Oculomotor ptosis
   Pupils
4. Trochlear retraction of eyelids
5. Abduscent:
   Squint
   Extra ocular Movement

6 Trigeminal Motor Sensory Motor
Reflexes
(Corneal/ Conjunctival/ Jaw)

7 Facial:

Elevation of Eyebrows
Frowning
Closure of Eyes
Nasolabial Fold
Deviation of .Angle of Mouth
Whistling
Taste on anterior 2/3rd of tongue

8. Vestibulo-cochlear

Acuity of hearing
Rinne's test
Weber's test

9. Glossopharvngeal:soft palate

10.Vagus: (Position, Movement, Reflex)
Pharyngeal wall movement, Gag Reflex

11. Spinal Accessory: Sternomastoid Action
Trapezius Action

12. Hypoglossal Tongue: wasting, fasciculation's, movements of Tongue

Motor System

	Upper limb		Lower limb	
	Right	left	Right	left
Nutrition				
Tone				
Power				
Coordination				
Abnormal Movements				

Sensory System

1 Superficial: Touch, Pain, and Temperature
2 Deep: Joint, Position Vibration
3 Cortical: Tactile Localisation.
Tactile Discrimination
Stereognosis

Reflexes	Right	Left
Superficial		
Corneal		
Conjuctival		
Abdominal		
Cremastric		
Plantar		
Deep		
Biceps		
Triceps		
Supinator		
Knee		
Ankle		

Signs of Meningeal irritation

Neck Rigidity
Kernig's Sign
Brudzinki's sign
Cerebellar Functions
Spine and cranium
Gait
Romberg's Sign
Peripheral Nerves

INVESTIGATIONS

1. Blood:
   - Hb%
   - TC, DC, ESR
   - Urea, Creatinine
   - Sugar
2. Chest X-Ray
3. Fundus
4. CSF:
   - Gross Appearance
   - Biochemical analysis (protein/glucose/chloride)
   - Cell counting and study
   - Microbiological study (grams stain/AFB/culture and sensitivity)
5. CSF Cortisol — Pre treatment / Post treatment
6. Blood culture:
7. CT Brain/MRI brain:

LIST OF ABBREVIATIONS USED

ACTH…….....Adrenocorticotropic Hormone

AFB..... …….Acid Fast Bacilli

ADH……Anti-Diuretic Hormone

ADA……Adenosine Deaminase

AIDS ..... ……Acquired immunodeficiency syndrome

ARP……Argyll-Robertson pupils

BCG ..... ……Bacille Calmette Guerin

CNS..... ……...Central Nervous System

CSF ..... ……Cerebrospinal fluid

DOTS…….....Directly Observed Treatment, Short course

EBV ..... ……..Epstein barr virus

FTA..... ……..Fluorescence treponemal antibody

FISH.....Fluorescence In Situ Hybridization

HAART…….....Highly Active Antiretroviral Therapy

HIV ....Human immunodeficiency virus

HPA……Hypothalamic-Pituitary Axis

HSV ..... ……...Herpes Simplex virus

IV……...Intra venous

LDH ..... ……Lactate dehydrogenase

MDR……..Multi Drug Resistant

MRC..... …..Medical Research Council

PCR..... ….Polymerase chain reaction

RIA..... …Radio Immuno Assay

SD ..... …Standard deviation

TBM..... ...Tuberculous Meningitis

VZV ....Varicella Zoster virus

VDRL..... ...Venereal disease research laboratory

ZN Stain.....Zeil Nelson stain

ICU.....Intensive Care Unit

WBC .....White Blood cells

KEY TO MASTER CHART

AFB……Acid fast bacilli

RBS……Random blood sugar

C/S…….. Culture& Sensitivity

CSF…….. Cerebrospinal fluid

Coding:

(+)…… present

(-)……... absent

Altered sensorium

1+……Drowsy

2+……Irritable

3+……Stupor

Seizures

1+…… One episode

2+…… Two episodes

3+……Three episodes

6+…… Six episodes

MASTER CHART

sl no	NAME	AGE	SEX	FEVER IN DAYS	VOMITTING	HEADACHE	ALTERED SENSORIUM	SEIZURES	MENINGEAL SIGNS	focal deficits	CELLS COUNT	NEUTROPHILS %	LYMPHOCYTES %	PROTIEN	SUGAR	RBS	CSF cortisol	post Rx cortisol	GRAMS STAIN	AFB	C/S of CSF	HIV STATUS	diagnosis
1	pavithra	19	F	4	+	+	3+	2+	+	+	200	90	10	112	34	140	15.2	1.9	positve	-	s.pneumoniae	-	Neutrophilic
2	mallika	45	F	3	+	+	-	-	+	-	130	80	20	80	60	150	14.5	1.4	-	-	-	-	Neutrophilic
3	balakrishna	23	M	2	-	+	1+	-	+	-	120	90	10	90	43	134	12.6	1	-	-	-	-	Neutrophilic
4	dhanalakshmi	46	F	3	+	+	-	-	+	-	140	90	10	98	45	124	11.9	1	-	-	-	-	Neutrophilic
5	veera kumar	20	M	2	-	+	-	-	+	-	160	85	15	110	48	160	13.4	1.3	-	-	-	-	Neutrophilic
6	babu	46	M	4	+	+	+	-	+	-	90	95	5	80	69	110	10.3	1.1	-	-	-	-	Neutrophilic
7	shalini	18	F	3	+	+	-	2 +	+	-	30	10	90	30	77	96	2.4	0.9	-	-	-	-	Aseptic
8	sumathi	17	F	3	+	-	2+	-	+	+	150	20	80	90	43	105	4.6	1.2	-	-	-	-	lymphocytic
9	dhanalakshmi	56	F	4	+	+	+	1+	+	-	230	10	90	114	30	112	5.2	1.5	-	-	-	-	lymphocytic
10	subramani	64	M	5	-	+	+	-	+	-	20	15	85	35	80	125	2.3	1.2	-	-	-	+	Aseptic
11	malar	40	F	4	+	-	-	1+	+	-	300	20	80	130	26	124	5	0.9	-	-	-	-	lymphocytic
12	valliammal	70	F	5	+	+	1+	-	+	-	50	10	90	70	58	94	3.1	1.4	-	-	-	-	Aseptic

13	shalini	54	F	4	+	-	1+	-	+	-	180	5	95	120	54	90	4.3	1.6	-	-	-	+	lym phocytic
14	surya	24	M	3	+	+	-	2+	+	-	230	90	10	140	30	130	14.4	0.7	-	-	n.men ingitidis	-	Neut rophilic
15	nias	20	m	4	+	+	2+	3+	+	-	400	80	20	160	26	144	16.8	1.1	+	-	H influ enza	-	Neut rophilic
16	murugan	45	M	2	+	-	1+	-	+	-	210	10	90	140	38	136	5.3	1.8	-	-	-	-	lymp hocytic
17	balachandran	33	M	5	+	+	-	-	+	-	190	—	100	130	29	98	5.4	1.3	-	-	-	-	lymp hocytic
18	acina	17	F	4	-	+	1+	1+	+	-	340	90	10	135	34	102	15.3	1	+	-	s.pneu moniae	-	Neut rophilic
19	gunamoorthy	40	M	3	+	-	-	2+	+	-	220	85	15	114	40	154	13.8	0.8	-	-	-	-	Neut rophilic
20	chandran	46	M	5	-	+	-	-	+	-	280	90	10	155	32	135	12.9	1.3	+	-	s.pne umoniae	-	Neutro philic
21	hariharan	17	M	3	+	+	2+	1+	+	-	30	—	100	30	78	124	2.1	1.2	-	-	-	-	Aseptic
22	senthil kumar	29	m	4	-	-	1+	-	+	+	200	10	90	135	50	200	3.9	0.9	-	-	-	-	lympho cytic
23	ravi	23	M	3	+	-	-	-	+	-	45	—	100	45	82	180	2.5	1	-	-	-	-	Aseptic
24	sundaran	17	m	2	+	+	1+	-	+	-	85	5	95	160	86	176	3.8	1.7	-	-	-	-	lymp hocytic
25	durga	21	F	2	+	+	1+	2+	+	-	160	80	20	105	40	202	11.2	1.4	-	-	-	-	Neutr ophilic
26	duraisamy	32	M	5	-	+	-	-	+	-	180	90	10	100	36	184	12	1.3	-	-	-	-	Neut rophilic

27	arun kumar	26	m	4	+	-	-	-	+	-	150	10	90	95	45	190	4.2	1.2	-	-	-	+	lymp hocytic
28	logeshwari	17	F	2	+	+	-	-	+	-	170	30	70	130	39	134	4	1.1	-	-	-	-	lymp hocytic
29	somu	22	M	3	-	+	2+	-	+	-	200	95	5	140	30	94	14.7	1.7	-	-	s.pneu moniae	-	Ne utrophilic
30	raghu	18	m	3	+	+	1+	-	+	-	140	2	98	110	46	178	4.6	1.9	-	-	-	-	lymp hocytic
31	ponnusamy	29	M	4	+	+	-	-	+	-	120	75	25	105	49	165	3.6	0.8	-	-	-	-	Neutr ophilic
32	sasi	35	M	4	-	-	1+	1+	+	+	230	15	85	125	48	204	4.5	0.9	-	-	-	-	lymph ocytic
33	govindasamy	65	M	5	+	+	-	2+	+	-	300	95	5	150	27	175	15.3	1	+	-	s.pneum oniae	-	Neut ophilic
34	selvaraj	39	M	4	-	-	-	-	+	-	35	—	100	35	66	96	2.4	1	-	-	-	-	Aseptic
35	uma maheswari	33	F	5	+	+	1+	-	+	-	120	10	90	90	36	102	4.7	1.3	-	-	-	-	lymp hocytic
36	kumarsamy	17	M	3	-	+	1+	-	+	-	300	95	5	165	37	90	14	1	-	-	n.men ingitidis	-	Neutr ophilic
37	jeyakodi	20	F	2	+	-	-	-	+	-	170	5	95	125	33	135	3.3	0.8	-	-	-	-	lymp hocytic
38	gunasekaran	16	M	2	+	+	-	-	+	+	20	—	100	30	77	115	2	1.2	-	-	-	-	Aseptic
39	keerthi vasan	17	M	3	+	-	3+	6+	+	-	200	10	90	105	39	146	4.8	1.1	-	-	-	-	lymp hocytic
40	baburan	40	M	4	+	-	-	1+	+	-	180	20	80	114	43	112	3.2	0.9	-	-	-	-	lymp hocytic

ஒப்புதல் படிவம்

பெயர் :

பாலினம் : வயது :

முகவரி :

அரசு கோவை மருத்துவக் கல்லூரியில் பொது மருத்துவ துறையில் பட்டமேற்படிப்பு பயிலும் மாணவன் அவர்கள் மேற்கொள்ளும் **"தண்டுவட திரவத்தில் கார்டிஸால் ஹார்மோன் அளவு கொண்டு பாக்டீரியாவினால் வரும் மூளைக்காய்ச்சலையும், பாக்டீரியா அல்லாத கிருமியினால் வரும் மூளைக்காய்ச்சலையும் வேறுபடுத்துதல் குறித்த ஆய்வு"** குறித்த ஆய்வில் செய்முறை மற்றும் அனைத்து விவரங்களையும் கேட்டுக் கொண்டு எனது சந்தேகங்களை தெளிவுப்படுத்திக் கொண்டேன் என்பதை தெரிவித்துக் கொள்கிறேன்.

நான் இந்த ஆய்வில் முழு சம்மதத்துடன், சுய சிந்தனையுடனும் கலந்து கொள்ள சம்மதிக்கிறேன்.

இந்த ஆய்வில் என்னுடைய அனைத்து விபரங்கள் பாதுகாக்கப்படுவதுடன் இதன் முடிவுகள் ஆய்விதழில் வெளியிடப்படுவதில் ஆட்சேபனை இல்லை என்பதை தெரிவித்துக் கொள்கிறேன். எந்த நேரத்திலும் இந்த ஆய்விலிருந்து நான் விலகிக் கொள்ள எனக்கு உரிமை உண்டு என்பதையும் அறிவேன்.

இடம் : கையொப்பம் / ரேகை

நாள் :