“ESTIMATION OF CSF CORTISOL LEVELS IN PATIENTS WITH MENINGITIS - A ONE YEAR CROSS-SECTIONAL STUDY”

REG NO. BG0111006

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.
in
GENERAL MEDICINE

DEPARTMENT OF MEDICINE,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
BELGAUM, KARNATAKA

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ENDORSEMENT

This is to certify that the dissertation entitled **"ESTIMATION OF CSF CORTISOL LEVELS IN PATIENTS WITH MENINGITIS - A ONE YEAR CROSS-SECTIONAL STUDY"** is a bonafide research work done by **THE CANDIDATE REG NO. BG0111006.**

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LIST OF ABBREVIATIONS USED

µL	-	Micro liter
ADA	-	American Diabetes Association
AFB	-	Acid-fast bacillus
AIDS	-	Aquired immunodefiency syndrome
APACHE	-	Acute Physiological Assessment for Chronic Health
BUN	-	Blood urea nitrogen
CBC	-	Complete blood count
CDC	-	Centers for Disease Control
cfu	-	Colony-forming units
CIE	-	Counterimmunoelectrophoresis
CMV	-	Cytomegalovirus
CNS	-	Central nervous system
COX	-	Cyclooxygenase
CSF	-	Cerebrospinal fluid
CT	-	Computed tomography
DIC	-	Disseminated intravascular coagulation
DNA	-	Deoxyribonucleic acid
e.g.	-	For example
EBV	-	Epstein-Barr virus
ED	-	Emergency department
ELISA	-	Enzyme-linked immunosorbent assay
ESBL	-	Extended spectrum β lactamases
FFP	-	Fresh frozen plasma
FNAC	-	Fine needle aspiration cytolocy
FTA-Abs	-	Fluorescent treponemal antibody absorption

GBS	-	Group B streptococcus
GI	-	Gastrointestinal
HHV	-	Human herpesvirus
HIb	-	Haemophilus influentiae type b
HIV	-	Human immunodeficiency virus
HLAR	-	High level aminoglycoside resistance
HSV	-	Herpes simplex virus
HSV	-	Herpesvirus
i.e.	-	That is
ICE	-	Immune-capture enzyme
ICP	-	Intracranial pressure
IL	-	Interleukin
IV	-	Intravenous
IVIg	-	Intravenous immunoglobulin
LCM	-	Lymphocytic choriomeningitis
LP	-	Lumbar puncture
mg/dL	-	Milligram per decilitre
MHA-TP	-	Microhemagglutination– T pallidum
mL	-	Millilitre
mm	-	Millimeter
MRI	-	Magnetic resonance imaging
MRSA	-	Methicillin resistant Staphylococcus aureus
MyD88	-	Myeloid differentiation 88
n	-	Total number
N. meningitidi	-	Nisseria meningitidis
NPEVs	-	Nnonpolio enteroviruses
NSAID	-	Non steroidal anti-inflammatory drugs

p	-	Probability
PAF	-	Platelet activation factor
PAM	-	Primary amebic meningoencephalitis
PCR	-	Polymerase chain reaction
PCT	-	Procalcitonin
PGE2	-	Prostaglandin E2
PMN	-	Polymorphonuclear
RNA	-	Ribonucleic acid
RPR	-	Rapid plasma reagent
SD	-	Standard deviation
SIADH	-	Syndrome of inappropriate secretion of antidiuretic hormone
TB	-	Tuberculosis
TLRs	-	Toll-like receptors
TNF	-	Tumour necrosis factor
TPHA	-	T pallidum hemagglutination
USA	-	United States of America
VDRL	-	Venereal Disease Research Laboratory
viz.	-	Namely
VZV	-	Varicella-zoster virus
WBC	-	White blood cells
Z – N	-	Ziehl – Neelsen
α	-	Alpha
β	-	Beta

ABSTRACT

Background and objectives

Increased CSF cortisol levels have previously been reported in various CNS disorders. The present study was planned to estimate CSF cortisol levels as a marker to differentiate the types of meningitis and to correlate CSF cortisol levels with severity.

Methodology

This one year cross-sectional study was carried out in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 50 patients presenting with meningitis aged more than 18 years were studied.

Results

In the present study 56% were males and 44% were females with male to female ratio of 1.2:1. The commonest age group was 31 to 45 years with 54% of the patients and the mean age was 36.10 ± 13.21 years. The commonest presentation was fever (94%) followed by headache (80%) and vomiting (72%). Signs of meningeal irritation were present in all the patients (100%). Altered consciousness and cerebellar signs were present in 36% and 26% of patients respectively. Neck stiffness was present in all the patients (100%) while Kernig and Brudzinki sign was noted among 94% and 18% of the patients. 40% of the patients had tubercular meningitis and 26% of the patients had viral meningitis. In the remaining acute pyogenic meningitis was present in 22%, fungal in 8% and toxoplasmosis in 4%.

Conclusion and interpretation

In this study the mean CSF cortisol levels were high in patients with tubercular meningitis (34.50 ± 8.45) compared to toxoplasmosis (25.50 ± 3.54), Acute pyogenic (Bacterial) (25.00 ± 6.99), fungal (20.00 ± 4.32) and viral (16.00 ± 7.93). This difference was statistically significant ($p<0.001$). Of the 31 patients with bacterial meningitis, 74.19% had elevated CSF cortisol ($p=0.007$). Patients with APACHE II score between 25 to 35, all (100%) patients had raised CSF cortisol levels ($p=0.041$). Out of 13 patients, 30.77% patients of viral meningitis had elevated CSF cortisol.

Keywords

Bacterial meningitis; CSF Cortisol; Meningitis; Toxoplasmosis;

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Chapter 1

Introduction

INTRODUCTION

Infections of the central nervous system (CNS) can be divided into 2 broad categories: those primarily involving the meninges (meningitis) and those primarily confined to the parenchyma (encephalitis). Meningitis is a clinical syndrome characterized by inflammation of the meninges, the three layers of membranes that enclose the brain and spinal cord. These layers consist of Dura - A tough outer membrane, Arachnoid - A lacy, weblike middle membrane and Subarachnoid space - A delicate, fibrous inner layer that contains many of the blood vessels that feed the brain and spinal cord.[1]

Meningitis is a life-threatening infection of the brain, especially on the protective membranes that cover the brain and spinal cord. These membranes are known as the meninges. They consist of three connective tissue layers which are the pia meter, the arachnoid and the dura mater. In the brain, three of them cooperate to support the blood vessels and contain the cerebrospinal fluid.[2]

The brain may be infected by bacteria, fungus or virus which will cause the inflammation of the meninges. Patients need to receive the treatment within a very short time because it is can be lethal.

The incidence rate of meningitis in developing countries such as Africa and India is higher than that in the developed countries by ten times since the access to preventive measures of the disease is still not well developed. Every year, there will be 8000 cases of meningitis and a total number of 2000 deaths occur that mark this disease as high morbidity and mortality. Between 1998 and 2003, there is a decline in the cases from 1.9 to 1.5 per 100,000 for the overall

incidence of bacterial meningitis. The decrease in the figure was partly contributed by the promoted use of the vaccination especially in many developed countries. In 1986, the median age for persons having infected by bacterial meningitis was 15 months, while in 1998, the median age has been changed to 25 years. This reveals that the disease has a higher frequency in adults than in children even though patients younger than 5 years old are at high risk to get the disease. For the adults, the incidences of bacterial meningitis are 1.7 to 7.2 cases per 100,000 every year and the mean annual incidence is 3.8 cases per 100,000.[2] The data on incidence of meningitis in India is scarce.[3]

There is a famous meningitis outbreak which is related to the meningococcal meningitis at the meningitis belt. The meningitis belt is an area of sub-Saharan Africa characterized by the dust winds and cold nights. Since meningococcal meningitis has seasonal variation, the dry season holds responsibility for large epidemics that occur in the meningitis belt.[4]

Meningitis can be classified further into three main groups based on the causative agents namely, bacterial meningitis, viral meningitis, and sub-acute meningitis. Bacterial meningitis is usually caused by Pneumococcal species, Haemophilus influenzae, Staphylococcal species, and meningococcal species. For nonbacterial meningitis, it is related to fungal and parasites that is frequently linked to etiologic agents like Cyptococcal species and Histoplasma species. In the aspect of viral meningitis, it can be Enterovirus meningitis or Herpes simplex virus meningitis.[2]

The bacteria causing meningitis is found in patients with chronic and debilitating diseases such as, diabetes mellitus, alcoholism, cirrhosis, hypogammaglobulinemia and complement deficiency.[5] These can be promoted through intimate and prolonged contact, for instance, kissing, sneezing or coughing on another person and staying very close to the infected person.[4]

There are a few common symptoms of meningitis, for instance, fever, headache, vomiting, altered mental status and neck stiffness. However, the classic triad of fever, neck stiffness and an altered mental status remains low among adults with community- acquired bacterial meningitis.[6]

It has been suggested that poor outcomes following bacterial meningitis are significantly influenced by exaggerated immune responses in the brain. The inflammatory brain injury has been associated with overproduction of reactive nitrogen species and tumour necrosis factor (TNF)-α in the intrathecal compartment.[7] Because proinflammatory responses play an important role in the pathogenesis of bacterial meningitis, their modulation may be an important component in the disease management (for review, see the report by Tauber and Moser.[8] Clinical trials have demonstrated that corticosteroids have efficacy in the treatment of bacterial meningitis caused by *Haemophilus influenzae* in children.[9] Recently, a beneficial effect of systemic administration of dexamethasone was documented in adults with bacterial meningitis caused by *Streptococcus pneumoniae*.[10]

The exact etiological diagnosis is often not possible, because of poor culture facilities, prior antibiotic therapy, delay in plating for culture, non-

availability of media with uniform quality, and low bacterial load. 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. Current microbiological tests are highly specific, but they lack sufficient sensitivity.[11]

Use of various biological markers in blood (C-reactive protein, white blood cell count [WBC], and procalcitonin) or cerebrospinal fluid [(CSF), protein, glucose, WBC, lactate, inflammatory cytokines)] has been suggested to improve sensitivity in determining the aetiological diagnosis.[12-16] 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.

Although it is known that exogenous corticosteroids can improve the outcome of bacterial meningitis, less is known about the role played by important endogenous anti-inflammatory mediators, such as cortisol and IL-10, in CSF during the course of bacterial meningitis. It is assumed that high levels of IL-10, as were observed in CSF from children with bacterial meningitis, can suppress the intensity of intrathecal inflammation and limit its deleterious effects.[17]

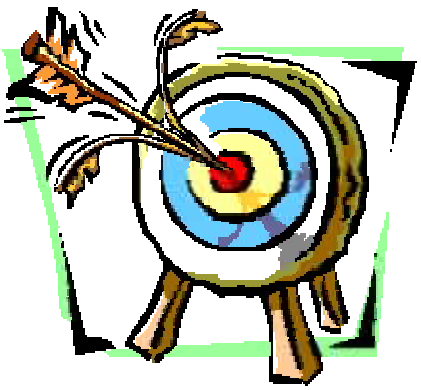
Although cortisol has effects similar to those of IL-10, no study of this hormone in the intrathecal compartment during bacterial meningitis has yet been reported in the literature. In contrast, elevated serum cortisol levels have been detected in several studies conducted in paediatric patients with a complicated course of bacterial meningitis.[18,19]

Moreover, unstimulated high cortisol levels in serum correlate with an unfavourable outcome of sepsis.[20] However, whether cortisol concentrations are also increased in CSF during bacterial meningitis and whether intrathecal levels of this hormone have prognostic value are not known.

Overall, meningitis is associated with significant morbidity and mortality and hence early diagnosis and severity is necessary to ensure appropriate management. Also, there are limited studies regarding the role of CSF cortisol levels in meningitis especially from India. Hence the present study was undertaken to estimate CSF cortisol levels as a marker to differentiate the types of meningitis and to correlate CSF cortisol levels with severity.

Chapter 2

Objectives



OBJECTIVES

The objectives of the study were;

1. Estimation of CSF cortisol levels as a marker to differentiate between types of meningitis.

2. Correlation of CSF cortisol to severity of meningitis.

Chapter 3

Review of Literature

REVIEW OF LITERATURE

Meningitis

The word "meningitis" comes from the Modern Latin word *meninga* and the Greek word *Menix* meaning "membrane". The suffix "itis" comes from the Greek word *itis* meaning "pertaining to". In medical English, the suffix "-itis means" "inflammation of". The membranes that surround the brain and the spinal cord are collectively known as the meninges - meningitis means inflammation of the meninges. According to Medilexicon's medical dictionary, meningitis is defined as Inflammation of the membranes of the brain or spinal cord.[21]

It is generally caused by infection of viruses, bacteria, fungi, parasites, and certain other organisms. Anatomical defects or weak immune systems may be linked to recurrent bacterial meningitis. In the majority of cases the cause is a virus. However, some non-infectious causes of meningitis also exist. And most of the time people become infected when they are in close contact with the discharges from the nose or throat of a person who is infected.[21]

Historical review

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

1806 : Danielson and Mann have given the first account of cerebrospinal meningitis in American literature.[22]

1810 : Reverend Foster gave a graphic description of an outbreak of meningococcemia and meningococcal meningitis.[22]

1863 : Cryptococcosis was recognized.[23]

1882 : The tubercle bacilli were discovered by Robert Koch.[24]

1887 : Weischselbaum described Nisseria meningitidis (N. meningitidis) as the causative agent of meningitis.[25]

1887 : Bruce grew brucella and named it Micrococcus melitensis.[22]

1890 : Bakten showed that meninges could be involved as a result of hematogenous spread.[22]

1891 : Quincke devised the diagnostic lumbar puncture.[22]

1893 : Licktheim isolated tubercle bacilli from CSF.[22]

1893 : Walter showed that the blood CSF barrier to bromide is altered in tuberculous meningitis.[22]

1894 : Cryptococcosis was described in more detail by Busse.[23]

1895 : The fungus was isolated from material of a patient by Busse.[23]

1897 : Bang isolated Brucella abortus.[22]

1913 : Simon Flexner first reported some success in treating bacterial meningitis with intrathecal equine meningococcal antiserum.[26]

1924 : Brucella was first isolated from a patient by Keefer in Baltimore.[22]

1932 : Burr and Finley studied the role of immunity in tuberculous meningitis by injecting tubercle protein in the cisterns of controls

and hypersensitive animals.[22]

1933 : Rich and Maccrodale challenged the hematogenous spread after doing autopsy studies and put forth the Rich focus theory.[22]

1933 : Lancefield introduced her technique for the precipitin grouping of Streptococci.[25]

1958 : Udani and Dastur showed that tuberculous meningitis could present in the form of encephalopathy. [22]

1969 : Dastur and Wadia showed that tuberculous meningitis could present as spinal arachnoiditis.[22]

1980 : Antonine Jesse noticed that tuberculous meningitis was more often associated with tuberculosis (TB) of other organs.[22]

Anatomy of meninges

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

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

The arachnoid mater is a thin transparent membrane that loosely surrounds the brain without dipping into its sulci. It bridges all irregularities of

the brain, with the exception of the longitudinal fissure and the stem of the lateral sulcus.

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

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

Cerebrospinal fluid

Formation and Absorption

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

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

Functions of CSF

- Supports the brain and cerebral venous sinuses.

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

CSF can be obtained by;

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

Lumbar puncture is the easiest method and is commonly used.

Lumbar puncture

Procedure

The patient lies with his/her back on the edge of the bed in the left lateral position with his/her knees drawn up. In adults, the L3 to L4 intervertebral space is marked. The part is cleaned with iodine and spirit and anaesthetized with 2% lignocaine. Then the spinal needle is inserted aiming towards the umbilicus. We feel resistance while passing through the spinal ligaments and dura mater. After passing through these structures, we notice reduced resistance as the needle enters the subarachnoid space. After withdrawing the stylet, CSF can be collected. After collecting the CSF, the needle is withdrawn and the puncture site is sealed with a tincture benzoin seal.[27,28]

Indications

Diagnostic

Absolute

Meningitis and subarachnoid haemorrhage.

Relative

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

Therapeutic

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

Contraindications

- Raised intracranial pressure
- Intracranial lesion with mass effect
- Clotting abnormalities
- Local infection

Complications

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

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

iii) Infections if proper aseptic precautions are not taken.

Epidemiology

Meningitides, whose aetiology is diversified, are very often caused by viruses such as the parotitis virus, less frequently by bacteria such as *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influentiae*. Other bacterial agents of meningitis can be Gram – (*Escherichia coli* and *Klebsiella enterobacter*) *group B Streptococci*, *positive coagulase Staphylococci*, *monocytogene Lysteria*, etc. Although these bacterial meningitides are less frequent they are potentially more serious than the viral ones.[29]

Invasive syndromes from *Haemophilus influentiae* are the most frequent cause of meningitis in less than five year- old children. They have considerably decreased in all countries where newborns are routinely vaccinated.[29]

The epidemiology of pneumococcal meningitides has not shown any appreciable variations in the last few years, whereas there is a definite increase in the incidence of meningococcal infections caused by serogroup C. As a matter of fact, there have been recent epidemics in some European countries. This phenomenon has implicated Great Britain (1999), Spain, Ukraine, Holland, Greece and France (2002).[29]

Meningococcal meningitis

Meningococcal meningitis is characterised by sudden onset, fever, headache, stiff neck, nausea, vomiting, there is frequently an urticarial exanthema that turns into maculopapular or petechial. The course of the infection can be particularly serious and can be accompanied by intravasal purpura coagulation, shock and death. The lethality varies from 5 to 15%. There are permanent consequences in approximately 1/5 surviving patients.[29]

The aetiological agent is the meningococcus, a diplococcus classified according to the characteristics of its capsular polysaccharides into 13 serogroups, A, B, C, D, 29E, H, I, K, L, X, Y, Z and W-135. The external membrane proteins, particularly class 2 and 3 ones, allow the identification of strain serotypes, whereas the serosubtypes can be identified by class 1 external membrane proteins. Finally, the wall lipopolysaccharides allow the identification of the immunotype.[30,31]

Transmission occurs through Flügge's droplets and, in most cases, the infection is characterised by rhinopharyngitis or it may progress asymptomatically. In a small percentage of cases the disease is very evident and it can also turn into sepsis. On average, the incubation time is 4 days but it may also reach as many as 10 days. The disease has very few consequences. The percentage distribution of those affected by the disease is 0-1% newborns, 25-40% children and 15-30% adults.[29]

Haemophilus influentiae type b (HIb) meningitis

Haemophilus Influentiae is a Gram-bacillococcus it is small, pleiomorphic, with six capsulated types (a-f) and acapsulated strains. The most important is type b (Hib). This serotype may cause meningitis, but also epiglottiditis, pneumonia, septic arthritis, pericarditis, etc. Hib is implicated in purulent meningitides. Hib meningitis affects children between 2 months and 5 years.[29]

The onset of the disease is usually sudden, with vomiting, lethargy, meningeal irritation, stiff neck and back. A state of coma and torpidity is frequent. Approximately 5% of the children affected by meningitis die even though subjected to antibiotic therapy, with neurological residues in as much as 20-35% of the cases. At the time of hospital discharge paralysis is reported in 11% of cases, long-term paralysis (permanent motorial alterations: hemiparesis, hemiparalysis, quadriplegia, ataxia, cerebral paralysis, spasticity) in 7%, convulsions in 8%; in addition, there are reports of hydrocephalus in 7%, visual deficit (up to blindness) in 4%, auditory deficit in 10%, language disorders in 15% and deficit in mental test performance after 2 years in 25% of the subjects (10-11% of the children with an I.Q. < 70). Hib is sensitive to cloramphenicol, cotrimoxazol and ampicillin (even though resistance to the latter drug is continuously increasing). Hib has been, in pre-vaccination times, the primary cause of bacterial meningitis.[29]

Pneumococcal meningitis

Every year in the United States the pneumococcus is responsible for 3000 cases of meningitis. The *S. pneumoniae* is a capsulated diplococcus. Depending on the different composition of the polysaccharide capsule more than 90 serotypes can be identified. The distribution of the serotypes is a function of age and geographical area. However, it seems that the most common strains, identified worldwide, are only 10-25 and are responsible for more than 80% of the invasive forms.[32-35]

The distribution of the cases of disease is 0.5% among newborns younger than one month, 10-20% among children and 40-50% among subjects older than 15 years.[29]

Global meningitis epidemiology

Meningococcal epidemics are still common in the poor countries of the planet. The meningococcus is frequently found in the mouth and throat. This microorganism may invade the circulatory stream and, having crossed the meninges, it can reproduce in the cerebrospinal fluid (CSF). This is followed by inflammation of the meninges. Sometimes the bacterium invades the circulatory stream causing a toxic shock. It is due to the release of a potent endotoxin, which stimulates the production of proteins such as the tumour necrosis factor (TNF). In turn these proteins determine an increase in the vascular permeability of the extremities, leading to an often-lethal collapse. If an antibiotic therapy is undertaken, the lethality oscillates from 3 to 10%. Extensive epidemics no longer occur in industrialized countries.[29]

Every year in the USA there are less than 3 cases/100,000 people. In the Sub-Saharan belt (meningitis belt) epidemics lasting several years occur every 5-12 years. It is possible to distinguish 12 *N. meningitides* serogroups on the basis of wall polysaccharides.[29]

Serogroup A is responsible for serious epidemics in Africa, China and Latin America. In Sub-Saharan countries epidemics are more frequent during the dry season. It has been estimated that in 1970-1992, in the meningitis belt (from Eritrea to Senegal), there were 800,000 cases of the disease.[31]

Furthermore, the World Health Organisation estimates that every year in the whole planet there are approximately 300,000 cases that cause 30,000 deaths and that 50-60% of the disease occurs among 3 to 5 year old children. While in Africa serogroup A is the most important one, in Europe, the United States and Australia serogroups B and C, responsible for 90% of cases, are the prevalent ones. Serogroups Y and W135 are ubiquitous, but they are rarely implicated in cases of invasive disease, even though in the Nineties an increase in the number of cases due to group Y was observed in Canada 7 while serogroup W135 meningococci have been responsible for a very severe epidemic in Saudi Arabia.[36]

In Europe the disease is concentrated among 1-4 year old children, serogroup B prevails in the total number of cases in 30 Nations, whereas it is serogroup C that more frequently results in septicaemia. In Germany the morbidity oscillates between 0.8 and 1.1/100,000 people. In this country the importance of serogroup C has varied during recent years (1997-1999),

oscillating from 0 to 37% of the cases, with a slight increase for subjects between 5 and 15 years. The highest rates of morbidity in Europe are observed in Ireland and Iceland (6 and 4 cases/100,000 people, respectively). It is for this reason that for several years an extensive vaccination campaign with the conjugated vaccine C has been underway in these countries.[33,34]

This vaccination program has also been introduced in Greece, Spain, the United Kingdom, etc. The pneumococcus is responsible for invasive diseases such as meningitis and sepsis affecting especially children and the elderly. In the USA the incidence of invasive diseases from pneumococcus in the early infancy is high, approximately 70 cases per 100,000 people. In Europe their frequency seems to be slightly lower than that of the United States, i.e. 8-25/100,000, even though the lower recourse to blood culture checks or rather the frequent use of antibiotics may partly explain the difference.[37] Still in the USA the annual incidence of pneumococcal meningitis is of 1-2 cases/100,000, with peaks in children between 6-24 months and in the elderly.[38]

Before the introduction of the conjugated anti-Hib vaccine, the highest incidence of the invasive diseases from Haemophilus was reported in Europe in the Scandinavian area, particularly Iceland (43 cases/100,000, in children up to 5 years). In the United Kingdom, where mass vaccination was introduced in 1992, the incidence dropped from 20 to 3 cases/100,000, after the 95% coverage was attained.[39]

A study was undertaken to study the trends in etiology and the antimicrobial resistance pattern of the pathogens prevalent in North India over a

period of 8 years. The study was performed from June 2001 to June 2009. CSF and blood samples were collected from all patients suspected of meningitis and inoculated on chocolate agar, blood agar and MacConkey agar. Antimicrobial susceptibility testing was done using Kirby Bauer disc diffusion method. Detection of methicillin resistant *Staphylococcus aureus* (MRSA), high level aminoglycoside resistance (HLAR) in *Enterococcus species*, extended spectrum β lactamases (ESBL), Amp C and metallo-betalactamases was also done. *Results:* 403 samples were positive on culture. *S. aureus* was the most common pathogen. Among the gram positive cocci as well as the gram negative bacilli, a gradual decline in the antimicrobial susceptibility was seen. The aminoglycosides had the best spectrum of antimicrobial activity. Towards the end of the study, an alarming rise of MRSA to 69.4%, HLAR among the *Enterococci* to 60% was noted. Among the *Enterobacteriaceae*, ESBL and Amp C production was found to be 16.7% and 42% respectively. No vancomycin and imipenem resistance was observed. Overall, an entirely different trend in etiology in bacterial meningitis was observed in the semitropical region of North India. The authors commented that, the high prevalence of drug resistant pathogens is a cause for worry and should be dealt with by rational use of antimicrobials.

Etiology

Causes of meningitis include bacteria, viruses, fungi, parasites, and drugs (eg, NSAIDs, metronidazole, and IV immunoglobulin [IVIg]). Certain risk factors are associated with particular pathogens.[40]

HIV infection increases susceptibility to meningitis from a variety of pathogens, including cryptococci, *Mycobacterium tuberculosis*, syphilis, and *Listeria* species. In addition, HIV itself may cause aseptic meningitis (see Meningitis in HIV).[40]

Other viral causes of meningitis include Enteroviruses, West Nile virus, Human herpesvirus (HHV)-2 and Lymphocytic choriomeningitis virus (LCM).[40]

In patients who have had trauma or neurosurgery, the most common microorganisms are *S pneumoniae* (if CSF leak is present), *Staphylococcus aureus*, enterobacteria, and *Pseudomonas aeruginosa*. In patients with an infected ventriculoperitoneal (atrial) shunt, the most common microorganisms are *Staphylococcus epidermidis, S aureus*, enterobacteria, *Propionibacterium acnes*, and diphtheroids (rare). Consultation with a neurosurgeon is indicated; early shunt removal is usually necessary for cure.[40]

Pachymeningitis

As indicated by the presence of abundant pus, pachymeningitis most often results from a bacterial infection (usually staphylococcal or streptococcal) that is localized to the dura. The organisms most often gain access to the meninges via a skull defect (eg, a skull fracture) or spread from an infection of the paranasal sinuses or cranial osteomyelitis.[40]

Haemophilus influenzae meningitis

H influenzae is a small, pleomorphic, gram-negative coccobacillus that is frequently found as part of the normal flora in the upper respiratory tract. The

organism can spread from one individual to another in airborne droplets or by direct contact with secretions. Meningitis is the most serious acute manifestation of systemic infection with *H influenzae*.[40]

In the past, *H influenzae* was a major cause of meningitis, and the encapsulated type b strain of the organism (Hib) accounted for the majority of cases. Since the introduction of Hib vaccine in the United States in 1990, the overall incidence of *H influenzae* meningitis has decreased by 35%, with Hib accounting for fewer than 9.4% of *H influenzae* cases.[41]

The isolation of *H influenzae* in adults suggests the presence of an underlying medical disorder, such as Paranasal sinusitis, Otitis media, Alcoholism, CSF leak after head trauma, Functional or anatomic asplenia and Hypogammaglobulinemia.[40]

Pneumococcal meningitis

S pneumoniae, a gram-positive coccus, is the most common bacterial cause of meningitis. In addition, it is the most common bacterial agent in meningitis associated with basilar skull fracture and CSF leak. It may be associated with other focal infections, such as pneumonia, sinusitis, or endocarditis (as, for example, in Austrian syndrome, which is the triad of pneumococcal meningitis, endocarditis, and pneumonia).[40]

S pneumoniae is a common colonizer of the human nasopharynx; it is present in 5-10% of healthy adults and 20-40% of healthy children. It causes meningitis by escaping local host defenses and phagocytic mechanisms, either

through choroid plexus seeding from bacteremia or through direct extension from sinusitis or otitis media. Patients with Hyposplenism, Hypogammaglobulinemia, Multiple myeloma, Glucocorticoid treatment, Defective complement (C1-C4), Diabetes mellitus, Renal insufficiency, Alcoholism, Malnutrition and Chronic liver disease are at increased risk for *S pneumoniae* meningitis.[40]

Streptococcus agalactiae meningitis

Streptococcus agalactiae (group B streptococcus [GBS]) is a gram-positive coccus that inhabits the lower GI tract. It also colonizes the female genital tract at a rate of 5-40%, which explains why it is the most common agent of neonatal meningitis (associated with 70% of cases). Predisposing risks in adults include Diabetes mellitus, Pregnancy, Alcoholism, Hepatic failure, Renal failure and Corticosteroid treatment. In 43% of adult cases, however, no underlying disease is present.[40]

Meningococcal meningitis

N meningitidis is a gram-negative diplococcus that is carried in the nasopharynx of otherwise healthy individuals. It initiates invasion by penetrating the airway epithelial surface. The precise mechanism by which this occurs is unclear, but recent viral or mycoplasmal infection has been reported to disrupt the epithelial surface and facilitate invasion by meningococcus.[40]

Most sporadic cases of meningococcal meningitis (95-97%) are caused by serogroups B, C, and Y, whereas the A and C strains are observed in epidemics

(< 3% of cases). Currently, *N meningitidis* is the leading cause of bacterial meningitis in children and young adults, accounting for 59% of cases.[40]

Risk factors for meningococcal meningitis include Deficiencies in terminal complement components (eg, membrane attack complex, C5-C9), which increases attack rates but is associated with surprisingly lower mortality rates, Properdin defects that increase the risk of invasive disease, Antecedent viral infection, chronic medical illness, corticosteroid use, and active or passive smoking and Crowded living conditions, as is observed in college dormitories (college freshmen living in dormitories are at highest risk) and military facilities, which has been reported in clustering of cases.[40]

Listeria monocytogenes meningitis

Listeria monocytogenes is a small gram-positive bacillus that causes 3% of bacterial meningitis cases and is associated with one of the highest mortalities (20%).[41] The organism is widespread in nature and has been isolated in the stool of 5% of healthy adults. Most human cases appear to be food-borne.

L monocytogenes is a common food contaminant, with a recovery rate of up to 70% from raw meat, vegetables, and meats. Outbreaks have been associated with consumption of contaminated coleslaw, milk, cheese, and alfalfa tablets. Groups at risk include Pregnant women, Infants and children, Elderly individuals (>60 years), Patients with alcoholism, Adults who are immunosuppressed (eg, steroid users, transplant recipients, or persons with AIDS), Individuals with chronic liver and renal disease, Individuals with diabetes and Persons with iron-

overload conditions (eg, hemochromatosis or transfusion-induced iron overload).[40]

Meningitis caused by gram-negative bacilli

Aerobic gram-negative bacilli include *Escherichia coli, Klebsiella pneumoniae, Serratia marcescens, P aeruginosa* and *Salmonella* species. Gram-negative bacilli can cause meningitis in certain groups of patients. *E coli* is a common agent of meningitis among neonates.[40]

Other predisposing risk factors for meningitis associated with gram-negative bacilli include Neurosurgical procedures or intracranial manipulation, Old age, Immunosuppression, High-grade gram-negative bacillary bacteremia and Disseminated strongyloidiasis.[40]

Disseminated strongyloidiasis has been reported as a classic cause of gram-negative bacillary bacteremia, as a result of the translocation of gut microflora with the *Strongyloides stercoralis* larvae during hyperinfection syndrome.[40]

Staphylococcal meningitis

Staphylococci are gram-positive cocci that are part of the normal skin flora. Meningitis caused by staphylococci is associated with risk factors such as neurosurgery, Head trauma, Presence of CSF shunts, Infective endocarditis and paraspinal infection.[40]

S epidermidis is the most common cause of meningitis in patients with CNS (ie, ventriculoperitoneal) shunts.[40]

Aseptic meningitis

Aseptic meningitis is one of the most common infections of the meninges. If appropriate diagnostic methods are employed, a specific viral etiology is identified in 50-60% of cases of aseptic meningitis. However, aseptic meningitis can also be caused by bacteria, fungi, and parasites. It is noteworthy that partially treated bacterial meningitis accounts for a large number of meningitis cases with a negative microbiologic workup.[40]

Infectious Agents Causing Aseptic Meningitis[40]

Category	Agent
Bacteria	Partially treated bacterial meningitis
	Listeria monocytogenes
	Brucella spp
	Rickettsia rickettsii
	Ehrlichia spp
	Mycoplasma pneumoniae
	Borrelia burgdorferi
	Treponema pallidum
	Leptospira spp
	Mycobacterium tuberculosis
	Nocardia spp
Parasites	*Naegleria fowleri*
	Acanthamoeba spp
	Balamuthia spp
	Angiostrongylus cantonensis
	Gnathostoma spinigerum
	Baylisascaris procyonis
	Strongyloides stercoralis
	Taenia solium (cysticercosis)

Category	Agent
Fungi	*Cryptococcus neoformans*
	Coccidioides immitis
	Blastomyces dermatitidis
	Histoplasma capsulatum
	Candida spp
	Aspergillus spp
Viruses	
Enterovirus	Poliovirus
	Echovirus
	Coxsackievirus A
	Coxsackievirus B
	Enterovirus 68-71
Herpesvirus (HSV)	HSV-1 and HSV-2
	Varicella-zoster virus
	Epstein-Barr virus
	Cytomegalovirus
	HHV-6 and HHV-7
Paramyxovirus	Mumps virus
	Measles virus
Togavirus	Rubella virus
Flavivirus	West Nile virus
	Japanese encephalitis virus
	St Louis encephalitis virus
Bunyavirus	California encephalitis virus
	La Crosse encephalitis virus
Alphavirus	Eastern equine encephalitis virus
	Western equine encephalitis virus
	Venezuelan encephalitis virus
Reovirus	Colorado tick fever virus
Arenavirus	LCM virus
Rhabdovirus	Rabies virus
Retrovirus	HIV

HHV = human herpesvirus; HSV = herpes simplex virus; LCM = lymphocytic choriomeningitis.

Enteroviruses account for of the majority of cases of aseptic meningitis in children, but West Nile virus and HSV-2 account for a substantial proportion of

cases in adults. The enteroviruses belong to the family Picornaviridae and are further classified as Poliovirus (3 serotypes); Coxsackievirus A (23 serotypes); Coxsackievirus B (6 serotypes); Echovirus (31 serotypes); Newly recognized enterovirus serotypes 68-71.[40]

Enteroviruses are usually spread by fecal-oral or respiratory routes. Infection occurs during summer and fall in temperate climates and year-round in tropical regions. The nonpolio enteroviruses (NPEVs) account for approximately 90% of cases of viral meningitis in which a specific pathogen can be identified. Echovirus 30 was reported as the cause of an epidemic in Japan in 1991. It was also reported as the cause of 20% of cases of aseptic meningitis reported to the Centers for Disease Control and Prevention (CDC) in 1991. The Herpesviridae family consists of large, DNA-containing enveloped viruses. Eight members are known to cause human infections, and all have been implicated in meningitis syndromes, with the exception of HHV-8 or Kaposi sarcoma–associated virus.[40]

HSV accounts for 0.5-3% of cases of aseptic meningitis; it is most commonly associated with primary genital infection and is less likely during recurrences. HSV-1 is a cause of encephalitis, while HSV-2 more commonly causes meningitis. Although Mollaret syndrome (a recurrent, but benign, aseptic meningitis syndrome) is more frequently associated with HSV-2, HSV-1 has also been implicated as a cause. Epstein-Barr virus (EBV, or HHV-4) and cytomegalovirus (CMV, or HHV-5) infection may manifest as meningitis in patients with the mononucleosis syndrome. Varicella-zoster virus (VZV, or HHV-3) and CMV cause meningitis in immunocompromised hosts, especially

patients with AIDS and transplant recipients. HHV-6 and HHV-7 have been reported to cause meningitis in transplant recipients.[40]

The most common arthropod-borne viruses are West Nile virus, St Louis encephalitis virus (a flavivirus), Colorado tick fever virus, and California encephalitis virus (bunyavirus group, including La Crosse encephalitis virus). St Louis encephalitis virus is a mosquito-borne flavivirus that may cause a febrile syndrome, aseptic meningitis syndrome, and encephalitis. Other members of the flavivirus group that may cause aseptic meningitis include tick-borne encephalitis virus and Japanese encephalitis virus.[40]

California encephalitis is a common childhood disease of the CNS that is caused by a virus in the genus *Bunyavirus*. Most of the cases of California encephalitis are probably caused by mosquito-borne La Crosse encephalitis virus. LCM virus is a member of the arenaviruses, a family of single-stranded, RNA-containing viruses in which rodents are the animal reservoir. The modes of transmission include aerosols and direct contact with rodents. Outbreaks have also been traced to infected laboratory mice and hamsters.[40]

The mumps virus is the most common cause of aseptic meningitis in unimmunized populations, occurring in 30% of all patients with mumps. Upon exposure, an incubation period of approximately 5-10 days ensues, followed by a nonspecific febrile illness and an acute onset of aseptic meningitis. This may be associated with orchitis, arthritis, myocarditis, and alopecia. Patients with acute HIV infection may present with aseptic meningitis syndrome, usually as part of the mononucleosislike acute seroconversion phenomenon. HIV should always be

suspected as a cause of aseptic meningitis in a patient with risk factors such as IV drug use or high-risk sexual behaviors. These patients will have negative results on HIV serologic tests (eg, enzyme-linked immunosorbent assay [ELISA] and Western blot); the diagnosis is made by the detection of serum HIV RNA on polymerase chain reaction (PCR) testing or of HIV p24 antigen.[40]

Adenovirus (serotypes 1, 6, 7, and 12) has been associated with cases of meningoencephalitis. Chronic meningoencephalitis has been reported with serotypes 7, 12, and 32. The infection is usually acquired through a respiratory route. Toscana virus meningitis or encephalitis should be considered in travelers returning from the a Mediterranean country (eg, Italy, Spain, or Greece) during the summer. Toscana viruses are transmitted by the bite of a sandfly. Toscana virus infection can be diagnosed by performing paired serologies and CSF PCR, which in the United States is available only through the CDC.[42]

Chronic meningitis

Chronic meningitis can be caused by a wide range of infectious and noninfectious etiologies.

Causes of Chronic Meningitis[40]

Category	Agent
Bacteria	*Mycobacterium tuberculosis*
	Borrelia burgdorferi
	Treponema pallidum
	Brucella spp
	Francisella tularensis
	Nocardia spp
	Actinomyces spp
Fungi	*Cryptococcus neoformans*
	Coccidioides immitis
	Blastomyces dermatitidis
	Histoplasma capsulatum
	Candida albicans
	Aspergillus spp
	Sporothrix schenckii
Parasites	*Acanthamoeba* spp
	Naegleria fowleri
	Angiostrongylus cantonensis
	Gnathostoma spinigerum
	Baylisascarisprocyonis
	Schistosoma spp
	Strongyloides stercoralis
	Echinococcus granulosus

Brucellae are small gram-negative coccobacilli that cause zoonoses as a result of infection with *Brucella abortus, Brucella melitensis, Brucella suis,* or *Brucella canis.* Transmission to humans occurs after direct or indirect exposure to infected animals (eg, sheep, goats, or cattle). Direct infection of the CNS

occurs in fewer than 5% of cases, with most patients presenting with acute or chronic meningitis. Persons at risk for brucellosis include individuals who had contact with infected animals or their products (eg, through intake of unpasteurized milk products). Veterinarians, abattoir workers, and laboratory workers dealing with these animals are also at risk.[40]

M tuberculosis is an acid-fast bacillus that causes a broad range of clinical illnesses that can affect virtually any organ of the body. It is spread through airborne droplet nuclei, and it infects one third of the world's population. Involvement of the CNS with tuberculous meningitis is usually caused by rupture of a tubercle into the subarachnoid space.[40]

Tuberculous meningitis should always be considered in the differential diagnosis of patients with aseptic meningitis or chronic meningitis syndromes, especially those with basilar meningitis, symptoms of more than 5 days' duration, or cranial nerve palsies. If tuberculous meningitis is suspected, antituberculosis therapy, with or without steroids, should be empirically started.[40]

Treponema pallidum is a slender, tightly coiled spirochete that is usually acquired by sexual contact. Other modes of transmission include direct contact with an active lesion, passage through the placenta, and blood transfusion (rare). *Borrelia burgdorferi*, a tick-borne spirochete, is the agent of Lyme disease, the most common vector-borne disease in the United States. Meningitis may be part of a triad of neurologic manifestations of Lyme disease that also includes cranial neuritis and radiculoneuritis. Lyme disease meningitis is typically associated with a facial palsy that can sometimes be bilateral.[40]

Cryptococcus neoformans is an encapsulated, yeastlike fungus that is ubiquitous. It has been found in high concentrations in aged pigeon droppings and pigeon nesting places. The 4 serotypes are designated A through D, with the A serotype causing most human infections. Onset of cryptococcal meningitis may be acute, especially among patients with AIDS. Numerous cases occur in healthy hosts (persons with no known T-cell defect); however, approximately 50-80% of cases occur in immunocompromised hosts. At particular risk are individuals with defects of T-cell–mediated immunity, such as persons with AIDS, organ transplant recipients, and other patients who use steroids, cyclosporine, and other immunosuppressants. Cryptococcal meningitis has also been reported in patients with idiopathic CD-4 lymphopenia, Hodgkin disease, sarcoidosis, and cirrhosis.[40]

Coccidioides immitis is a soil-based, dimorphic fungus that exists in mycelial and yeast (spherule) forms. Persons at risk for coccidioidal meningitis include individuals exposed to the endemic regions (tourists and local populations) and those with immune deficiency (persons with AIDS and organ transplant recipients).[40]

Blastomyces dermatitidis is a dimorphic fungus that has been reported to be endemic in North America (in the Mississippi and Ohio River basins). It has also been isolated from parts of Central America, South America, the Middle East, and India. Its natural habitat is not well defined. Soil that is rich in decaying matter and environments around riverbanks and waterways have been demonstrated to harbor *B dermatitidis* during outbreaks and are thought to be risk factors for acquiring the infection.[40]

Inhalation of the conidia establishes a pulmonary infection. Dissemination may occur in certain individuals, including those with underlying immune deficiency (from HIV or pharmaceutical agents) and extremes of age, and may involve the skin, bones and joints, genitourinary tract, and CNS. Involvement of the CNS occurs in fewer than 5% of cases.[40]

Histoplasma capsulatum is one of the dimorphic fungi that exist in mycelial and yeast forms. It is usually found in soil and can occasionally cause a chronic meningitis. The preferred means of making the diagnosis is CSF histoplasma antigen detection.[40]

Candida species are ubiquitous in nature. They are normal commensals in humans and are found in the skin, the GI tract, and the female genital tract. The most common species is *Candida albicans*, but the incidence of non-*albicans* candidal infections (*Candida tropicalis*) is increasing, including species with antifungal resistance (*Candida krusei* and *Candida glabrata*). Involvement of the CNS usually follows hematogenous dissemination. The most important predisposing risks for acquiring disseminated candidal infection appear to be iatrogenic (the administration of broad-spectrum antibiotics and the use of indwelling devices such as urinary and vascular catheters). Prematurity in neonates is considered a predisposing risk factor as well. Infection may also follow neurosurgical procedures, such as placement of ventricular shunts.[40]

Sporothrix schenckii is an endemic dimorphic fungus that is often isolated from soil, plants, and plant products. Human infections are characteristically lymphocutaneous. Extracutaneous manifestations of sporotrichosis may occur,

though meningeal sporotrichosis, which is the most severe form, is a rare complication. AIDS is a reported underlying risk factor in many described cases and is associated with a poor outcome. Infection with free-living amebas is an infrequent but often life-threatening human illness, even in immunocompetent individuals. *N fowleri* is the only species of *Naegleria* recognized to be pathogenic in humans, and it is the agent of primary amebic meningoencephalitis (PAM). The parasite has been isolated in lakes, pools, ponds, rivers, tap water, and soil.[40]

Infection occurs when a person is swimming or playing in contaminated water sources (eg, inadequately chlorinated water and sources associated with poor decontamination techniques). The *N fowleri* amebas invade the CNS through the nasal mucosa and cribriform plate. PAM occurs in 2 forms. The first is characterized by an acute onset of high fever, photophobia, headache, and altered mental status, similar to bacterial meningitis, occurring within 1 week after exposure. Because it is acquired via the nasal area, olfactory nerve involvement may manifest as abnormal smell sensation. Death occurs in 3 days in patients who are not treated. The second form, the subacute or chronic form, consists of an insidious onset of low-grade fever, headache, and focal neurologic signs. Duration of illness is weeks to few months.[40]

Acanthamoeba and *Balamuthia* cause granulomatous amebic encephalitis, which is a subacute opportunistic infection that spreads hematogenously from the primary site of infection (skin or lungs) to the CNS and causes an encephalitis syndrome. These cases can be difficult to distinguish from culture-negative meningitis.[40]

Angiostrongylus cantonensis, the rat lungworm, can cause eosinophilic meningitis (pleocytosis with more than 10% eosinophils) in humans. The adult parasite resides in the lungs of rats. Its eggs hatch, and the larval stages are expelled in the feces. The larvae develop in the intermediate host, usually land snails, freshwater prawns, and crabs. Humans acquire the infection by ingesting raw mollusks.[40]

Gnathostoma spinigerum, a GI parasite of wild and domestic dogs and cats, may cause eosinophilic meningoencephalitis. Humans acquire the infection after ingesting undercooked infected fish and poultry.[40]

Baylisascaris procyonis is an ascarid parasite that is prevalent in the raccoon populations in the United States and rarely causes human eosinophilic meningoencephalitis. Human infections occur after accidental ingestion of food products contaminated with raccoon feces.[40]

Additional causes of meningitis

Congenital malformation of the stapedial footplate has been implicated in the development of meningitis. Head and neck surgery, penetrating head injury, comminuted skull fracture, and osteomyelitic erosion may infrequently result in direct implantation of bacteria into the meninges. Skull fractures can tear the dura and cause a CSF fistula, especially in the region of the frontal ethmoid sinuses. Patients with any of these conditions are at risk for bacterial meningitis.[40]

Pathophysiology

Most cases of meningitis are caused by an infectious agent that has colonized or established a localized infection elsewhere in the host. Potential sites of colonization or infection include the skin, the nasopharynx, the respiratory tract, the gastrointestinal (GI) tract, and the genitourinary tract. The organism invades the submucosa at these sites by circumventing host defenses (eg, physical barriers, local immunity, and phagocytes or macrophages). An infectious agent (ie, a bacterium, virus, fungus, or parasite) can gain access to the CNS and cause meningeal disease via any of the 3 following major pathways:

- Invasion of the bloodstream (ie, bacteremia, viremia, fungemia, or parasitemia) and subsequent hematogenous seeding of the CNS.

- A retrograde neuronal (eg, olfactory and peripheral nerves) pathway (eg, *Naegleria fowleri* or *Gnathostoma spinigerum*)

- Direct contiguous spread (eg, sinusitis, otitis media, congenital malformations, trauma, or direct inoculation during intracranial manipulation).[40]

Invasion of the bloodstream and subsequent seeding is the most common mode of spread for most agents. This pathway is characteristic of meningococcal, cryptococcal, syphilitic, and pneumococcal meningitis. Rarely, meningitis arises from invasion via septic thrombi or osteomyelitic erosion from infected contiguous structures. Meningeal seeding may also occur with a direct bacterial inoculate during trauma, neurosurgery, or instrumentation. Meningitis in the

newborn may be transmitted vertically, involving pathogens that have colonized the maternal intestinal or genital tract, or horizontally, from nursery personnel or caregivers at home.[40]

Local extension from contiguous extracerebral infection (eg, otitis media, mastoiditis, or sinusitis) is a common cause. Possible pathways for the migration of pathogens from the middle ear to the meninges include the bloodstream, preformed tissue planes (posterior fossa), temporal bone fractures and the oval or round window membranes of the labyrinths.[40]

The brain is naturally protected from the body's immune system by the barrier that the meninges create between the bloodstream and the brain. Normally, this protection is an advantage because the barrier prevents the immune system from attacking the brain. However, in meningitis, the blood-brain barrier can become disrupted; once bacteria or other organisms have found their way to the brain, they are somewhat isolated from the immune system and can spread.[40]

When the body tries to fight the infection, the problem can worsen; blood vessels become leaky and allow fluid, WBCs, and other infection-fighting particles to enter the meninges and brain. This process, in turn, causes brain swelling and can eventually result in decreasing blood flow to parts of the brain, worsening the symptoms of infection.[43]

Depending on the severity of bacterial meningitis, the inflammatory process may remain confined to the subarachnoid space. In less severe forms, the pial barrier is not penetrated, and the underlying parenchyma remains intact.

However, in more severe forms of bacterial meningitis, the pial barrier is breached, and the underlying parenchyma is invaded by the inflammatory process. Thus, bacterial meningitis may lead to widespread cortical destruction, particularly when left untreated. Replicating bacteria, increasing numbers of inflammatory cells, cytokine-induced disruptions in membrane transport, and increased vascular and membrane permeability perpetuate the infectious process in bacterial meningitis. These processes account for the characteristic changes in CSF cell count, pH, lactate, protein, and glucose in patients with this disease. Exudates extend throughout the CSF, particularly to the basal cisterns, resulting in the following:[40]

- Damage to cranial nerves (eg, cranial nerve VIII, with resultant hearing loss)
- Obliteration of CSF pathways (causing obstructive hydrocephalus)
- Induction of vasculitis and thrombophlebitis (causing local brain ischemia)

Intracranial pressure and cerebral fluid

One complication of meningitis is the development of increased intracranial pressure (ICP). The pathophysiology of this complication is complex and may involve many proinflammatory molecules as well as mechanical elements. Interstitial edema (secondary to obstruction of CSF flow, as in hydrocephalus), cytotoxic edema (swelling of cellular elements of the brain through the release of toxic factors from the bacteria and neutrophils), and

vasogenic edema (increased blood brain barrier permeability) are all thought to play a role.[40]

Without medical intervention, the cycle of decreasing CSF, worsening cerebral edema, and increasing ICP proceeds unchecked. Ongoing endothelial injury may result in vasospasm and thrombosis, further compromising CSF, and may lead to stenosis of large and small vessels. Systemic hypotension (septic shock) also may impair CSF, and the patient soon dies as a consequence of systemic complications or diffuse CNS ischemic injury.[40]

Cerebral edema

The increased CSF viscosity resulting from the influx of plasma components into the subarachnoid space and diminished venous outflow lead to interstitial edema. The accumulation of the products of bacterial degradation, neutrophils, and other cellular activation leads to cytotoxic edema. The ensuing cerebral edema (ie, vasogenic, cytotoxic, and interstitial) significantly contributes to intracranial hypertension and a consequent decrease in cerebral blood flow. Anaerobic metabolism ensues, which contributes to increased lactate concentration and hypoglycorrhachia. In addition, hypoglycorrhachia results from decreased glucose transport into the spinal fluid compartment. Eventually, if this uncontrolled process is not modulated by effective treatment, transient neuronal dysfunction or permanent neuronal injury results.[40]

Cytokines and secondary mediators in bacterial meningitis

Key advances in understanding the pathophysiology of meningitis include insight into the pivotal roles of cytokines (eg, tumor necrosis factor alpha [TNF-α] and interleukin [IL]-1), chemokines (IL-8), and other proinflammatory molecules in the pathogenesis of pleocytosis and neuronal damage during occurrences of bacterial meningitis. Increased CSF concentrations of TNF-α, IL-1, IL-6, and IL-8 are characteristic findings in patients with bacterial meningitis. Cytokine levels, including those of IL-6, TNF-α, and interferon gamma, have been found to be elevated in patients with aseptic meningitis. The proposed events involving these inflammation mediators in bacterial meningitis begin with the exposure of cells (eg, endothelial cells, leukocytes, microglia, astrocytes, and meningeal macrophages) to bacterial products released during replication and death; this exposure incites the synthesis of cytokines and proinflammatory mediators. This process is likely initiated by the ligation of the bacterial components (eg, peptidoglycan and lipopolysaccharide) to pattern-recognition receptors, such as the Toll-like receptors (TLRs).[40]

TNF-α and IL-1 are most prominent among the cytokines that mediate this inflammatory cascade. TNF-α is a glycoprotein derived from activated monocyte-macrophages, lymphocytes, astrocytes, and microglial cells. IL-1, previously known as endogenous pyrogen, is also produced primarily by activated mononuclear phagocytes and is responsible for the induction of fever during bacterial infections. Both IL-1 and TNF-α have been detected in the CSF of individuals with bacterial meningitis. In experimental models of meningitis, they appear early during the course of disease and have been detected within 30-

45 minutes of intracisternal endotoxin inoculation. Many secondary mediators, such as IL-6, IL-8, nitric oxide, prostaglandins (eg, prostaglandin E2 [PGE2]), and platelet activation factor (PAF), are presumed to amplify this inflammatory event, either synergistically or independently. IL-6 induces acute-phase reactants in response to bacterial infection. The chemokine IL-8 mediates neutrophil chemoattractant responses induced by TNF-α and IL-1.[40]

Nitric oxide is a free radical molecule that can induce cytotoxicity when produced in high amounts. PGE2, a product of cyclooxygenase (COX), appears to participate in the induction of increased blood-brain barrier permeability. PAF, with its myriad biologic activities, is believed to mediate the formation of thrombi and the activation of clotting factors within the vasculature. However, the precise roles of all these secondary mediators in meningeal inflammation remain unclear. The net result of the above processes is vascular endothelial injury and increased blood-brain barrier permeability, leading to the entry of many blood components into the subarachnoid space. In many cases, this contributes to vasogenic edema and elevated CSF protein levels. In response to the cytokines and chemotactic molecules, neutrophils migrate from the bloodstream and penetrate the damaged blood-brain barrier, producing the profound neutrophilic pleocytosis characteristic of bacterial meningitis.[40]

Genetic predisposition to inflammatory response

The inflammatory response and the release of proinflammatory mediators are critical to the recruitment of excess neutrophils to the subarachnoid space.

These activated neutrophils release cytotoxic agents, including oxidants and metalloproteins that cause collateral damage to brain tissue.[40]

Pattern recognition receptors, of which TLR A4 (TLRA4) is the best studied, lead to increase in the myeloid differentiation 88 (MyD88)-dependent pathway and excess production of proinflammatory mediators. At present, dexamethasone is used to decrease the effects of cellular toxicity by neutrophils after they are present. Researchers are actively seeking ways of inhibiting TLRA4 and other proinflammatory recognition receptors through genetically engineered suppressors.[44]

Bacterial seeding

Bacterial seeding of the meninges usually occurs through hematogenous spread. In patients without an identifiable source of infection, local tissue and bloodstream invasion by bacteria that have colonized the nasopharynx may be a common source. Many meningitis-causing bacteria are carried in the nose and throat, often asymptomatically. Most meningeal pathogens are transmitted through the respiratory route, including *Neisseria meningitidis* (meningococcus) and *S pneumoniae* (pneumococcus). Certain respiratory viruses are thought to enhance the entry of bacterial agents into the intravascular compartment, presumably by damaging mucosal defenses. Once in the bloodstream, the infectious agent must escape immune surveillance (eg, antibodies, complement-mediated bacterial killing, and neutrophil phagocytosis).[40]

Subsequently, hematogenous seeding into distant sites, including the CNS, occurs. The specific pathophysiologic mechanisms by which the infectious

agents gain access to the subarachnoid space remain unclear. Once inside the CNS, the infectious agents likely survive because host defenses (eg, immunoglobulins, neutrophils, and complement components) appear to be limited in this body compartment.[40]

Presentation

History

Only about 44% of adults with bacterial meningitis exhibit the classic triad of fever, headache, and neck stiffness.[45] These symptoms can develop over several hours or over 1-2 days. In a large prospective study of 696 cases of adults with bacterial meningitis, van de Beek et al reported that 95% of the patients had 2 out of the following 4 symptoms: fever, headache, stiff neck, and altered mental status.[45]

Other symptoms can include Nausea, Vomiting, Photalgia (photophobia) - Discomfort when the patient looks into bright lights, Sleepiness, Confusion, Irritability, Delirium and Coma. Approximately 25% of patients with bacterial meningitis present acutely, well within 24 hours of the onset of symptoms. Occasionally, if a patient has been taking antibiotics for another infection, meningitis symptoms may take longer to develop or may be less intense.[40]

Approximately 25% of patients have concomitant sinusitis or otitis that could predispose to *S pneumoniae* meningitis.[45] In contrast, patients with subacute bacterial meningitis and most patients with viral meningitis present with neurologic symptoms developing over 1-7 days. Chronic symptoms lasting

longer than 1 week suggest the presence of meningitis caused by certain viruses or by tuberculosis, syphilis, fungi (especially cryptococci), or carcinomatosis.[40]

Patients with viral meningitis may have a history of preceding systemic symptoms (eg, myalgias, fatigue, or anorexia). Patients with meningitis caused by the mumps virus usually present with the triad of fever, vomiting, and headache. This follows the onset of parotitis (salivary gland enlargement occurs in 50% of patients), which clinically resolves in 7-10 days. As bacterial meningitis progresses, patients of any age may have seizures (30% of adults and children; 40% of newborns and infants). In patients who have previously been treated with oral antibiotics, seizures may be the sole presenting symptom; fever and changes in level of alertness or mental status are less common in partially treated meningitis than in untreated meningitis.[40]

Atypical presentation may be observed in certain groups. Elderly individuals, especially those with underlying comorbidities (eg, diabetes, renal and liver disease), may present with lethargy and an absence of meningeal symptoms. Patients with neutropenia may present with subtle symptoms of meningeal irritation. Other immunocompromised hosts, including organ and tissue transplant recipients and patients with HIV and AIDS, may also have an atypical presentation. Immunosuppressed patients may not show dramatic signs of fever or meningeal inflammation.[40]

A less dramatic presentation headache, nausea, minimal fever, and malaise may be found in patients with low-grade ventriculitis associated with a ventriculoperitoneal shunt. Newborns and small infants also may not present with

the classic symptoms, or the symptoms may be difficult to detect. An infant may appear only to be slow or inactive, or be irritable, vomiting, or feeding poorly. Other symptoms in this age group include temperature instability, high-pitched crying, respiratory distress, and bulging fontanelles (a late sign in one third of neonates). Epidemiologic factors and predisposing risks should be assessed in detail. These may suggest the specific etiologic agent.[40]

- The classic clinical triad of meningitis is fever, headache and nuchal rigidity (stiff neck)
- Alteration in mental status
- Nausea, vomiting and photophobia
- Seizures
- Deteriorating or reduced level of consciousness, papilledema, dilated poorly reactive pupils, sixth nerve palsy, decerebrate posturing, bradycardia, hypertension and irregular respirations, signs of raised intracranial pressure.
- Focal neurological deficits like hemiplegia, cranial nerve palsies.
- Other non-specific features like malaise, myalgia, anorexia, abdominal pain and /or diarrhea, lethargy.
- Specific clinical features depending upon the etiology like – a petechial or purpuric rash or large ecchymoses in meningococcal meningitis.

Signs of Meningeal Irritation[40]

- Neck retraction
- Arching of the back (opisthotonos)

- Curling of the body away from the light

Neck rigidity/Neck stiffness

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

Kernig's Sign

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

Brudzinski's Sign

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

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

Pathological and Clinical correlations in acute, subacute and chronic meningeal reactions[40]

I. In acute meningeal inflammation

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

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

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

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

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

II. In more subactue and chronic forms of meningitis

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

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

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

III. Late effects or sequelae

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

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

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

Diagnosis

The diagnostic challenges in patients with clinical findings of meningitis are early identification and treatment of patients with acute bacterial meningitis, assessing whether a treatable central nervous system (CNS) infection is present in those with suspected subacute or chronic meningitis and Identifying the causative organism. Bacterial meningitis must be the first and foremost consideration in the differential diagnosis of patients with headache, neck stiffness, fever, and altered mental status. Acute bacterial meningitis is a medical emergency, and delays in instituting effective antimicrobial therapy result in increased morbidity and mortality.[40]

In general, whenever the diagnosis of meningitis is strongly considered, a lumbar puncture should be promptly performed. Examination of the cerebrospinal fluid (CSF) is the cornerstone of the diagnosis. The diagnosis of bacterial meningitis is made by culture of the CSF sample. The opening pressure should be measured and the fluid sent for cell count (and differential count), chemistry (ie, CSF glucose and protein), and microbiology (ie, Gram stain and cultures).[40]

A concern regarding LP is that the lowering of CSF pressure from withdrawal of CSF could precipitate herniation of the brain. Herniation can sometimes occur in acute bacterial meningitis and other CNS infections as the consequence of severe cerebral edema or acute hydrocephalus. Clinically, this is manifested by an altered state of consciousness, abnormalities in pupil reflexes, and decerebrate or decorticate posturing. The incidence of herniation after LP, even in patients with papilledema, is approximately 1%.[40]

A screening computed tomography (CT) scan of the head may be performed before LP to determine the risk of herniation.[46] The factors included in the Infectious Diseases Society of America guidelines helps to decide who should undergo CT before LP.[47]

Other laboratory tests, which may include blood cultures, are needed to complement the CSF culture. These bacterial cultures are used for identification of the offending bacteria and occasionally its serogroup, as well as for determination of the organism's susceptibility to antibiotics. Special studies, such as serology and nucleic acid amplification, may also be performed, depending on

clinical suspicion of an offending organism. As many as 50% of patients with pneumococcal meningitis also have evidence of pneumonia on initial chest radiography. This association occurs in fewer than 10% of patients with meningitis caused by *H influenzae* or *N meningitidis* and in approximately 20% of patients with meningitis caused by other organisms.[40]

Blood Studies

In patients with bacterial meningitis, a complete blood count (CBC) with differential will demonstrate polymorphonuclear leukocytosis with a left shift. Useful elements of the metabolic panel include the following:[40]

- Serum electrolytes, to determine dehydration or syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
- Serum glucose (which is compared with the CSF glucose)
- Blood urea nitrogen (BUN) or creatinine and liver profile, to assess organ function and adjust antibiotic dosing

The serum glucose level may be low if glycogen stores are depleted, or they may be high in infected patients with diabetes. A coagulation profile and platelet count are indicated in cases of chronic alcohol use, chronic liver disease, or suspected disseminated intravascular coagulation (DIC). Patients with coagulopathies may require platelets or fresh frozen plasma (FFP) before LP.

Cultures and Bacterial Antigen Testing[40]

Obtaining cultures before instituting antibiotics may be helpful if the diagnosis is uncertain. The utility of cultures is most evident when LP is delayed until head imaging can rule out the risk of brain herniation, in which cases antimicrobial therapy is rightfully initiated before CSF samples can be obtained. These cultures include the following:

- Blood - 50% positive in meningitis caused by *H influenzae, S pneumoniae,* or *N meningitides*
- Nasopharynx
- Respiratory secretions
- Urine
- Skin lesions

Latex agglutination or counterimmunoelectrophoresis (CIE) of blood, urine, and CSF for specific bacterial antigens is occasionally recommended if diagnosis is challenging or in patients with partially treated meningitis. The Binax NOW *S pneumoniae* antigen test, if done on CSF, has a 99%-100% sensitivity and specificity and can even be positive despite prior antibiotic therapy.[48]

The use of nucleic acid amplification (eg, polymerase chain reaction [PCR] testing) has revolutionized the diagnosis of herpes simplex virus (HSV) meningitis. The availability of this technique has confirmed HSV as the cause of

the recurrent Mollaret meningitis. This technique has also been applied to the diagnosis of enteroviral infections and the other herpesvirus infections. The PCR assay for enteroviruses has been demonstrated to be substantially more sensitive than culture and is 94-100% specific.

Syphilis Testing[40]

Perform serologic tests to detect syphilis. Screening for syphilis is done with the nontreponemal tests: rapid plasma reagent (RPR) or Venereal Disease Research Laboratory (VDRL). Positive results are confirmed with one of the following specific treponemal tests:

- Fluorescent treponemal antibody absorption (FTA-Abs)
- *T pallidum* hemagglutination (TPHA)
- Microhemagglutination– *T pallidum* (MHA-TP)
- The newer immune-capture enzyme immunoassay (ICE Syphilis) recombinant antigen test

In patients with syphilis, initial results on nontreponemal tests can serve as a baseline for gauging the success of therapy. Titers decrease and usually revert to negative or undetectable levels following effective treatment.

Serum Procalcitonin Testing[40]

Increasing data suggest that serum procalcitonin (PCT) levels can be used as a guide to distinguish between bacterial and aseptic meningitis in children.

Elevated serum PCT levels predict bacterial meningitis. The results of serum PCT testing, combined with other findings, could be helpful in making clinical decisions.[49]

In an analysis of retrospective, multicenter, hospital-based cohort studies, Dubos et al confirmed that measurement of the PCT level is the best biologic marker for differentiating bacterial meningitis from aseptic meningitis in children in the emergency department (ED). With a threshold of 0.5 ng/mL, the sensitivity and specificity of the PCT level in distinguishing between bacterial and aseptic meningitis were 99% and 83%, respectively.[49]

Lumbar Puncture and CSF Analysis[40]

Elevated opening pressure correlates with increased risk of morbidity and mortality in bacterial and fungal meningitis. In bacterial meningitis, elevated opening pressure (reference range, 80-200 mm H_2 O) suggests increased intracranial pressure (ICP) from cerebral edema. In viral meningitis, the opening pressure is usually within the reference range. The CSF opening pressure may be elevated at times in cryptococcal meningitis, suggesting increased ICP, and it is usually elevated in tuberculous meningitis. The CSF cell count varies according to the offending pathogen (see Tables 5 and 6 below). It is usually in the few hundreds (100-1000/µL) with a predominance of lymphocytes in patients with viral meningitis. Some cases of echovirus, mumps, and HSV meningitis may produce a neutrophilic picture early in the course of disease.

CSF Findings in Meningitis by Etiologic Agent[40]

Agent	Opening Pressure (mm H_2O)	WBC count (cells/µL)	Glucose (mg/dL)	Protein (mg/dL)	Microbiology
Bacterial meningitis	200-300	100-5000; >80% PMNs	< 40	>100	Specific pathogen demonstrated in 60% of Gram stains and 80% of cultures
Viral meningitis	90-200	10-300; lymphocytes	Normal, reduced in LCM and mumps	Normal but may be slightly elevated	Viral isolation, PCR assays
Tuberculous meningitis	180-300	100-500; lymphocytes	Reduced, < 40	Elevated, >100	Acid-fast bacillus stain, culture, PCR
Cryptococcal meningitis	180-300	10-200; lymphocytes	Reduced	50-200	India ink, cryptococcal antigen, culture
Aseptic meningitis	90-200	10-300; lymphocytes	Normal	Normal but may be slightly elevated	Negative findings on workup
Normal values	80-200	0-5; lymphocytes	50-75	15-40	Negative findings on workup

LCM = lymphocytic choriomeningitis; PCR = polymerase chain reaction; PMN = polymorphonuclear leukocyte; WBC = white blood cell.

Comparison of CSF Findings by Type of Organism[40]

Normal Finding	Bacterial Meningitis	Viral Meningitis*	Fungal Meningitis**
Pressure (mm H_2 O) 50-150	Increased	Normal or mildly increased	Normal or mildly increased in tuberculous meningitis; may be increased in fungal; AIDS patients with cryptococcal meningitis have increased risk of blindness and death unless kept below 300 mm H_2 O
Cell count (mononuclear cells/µL) Preterm: 0-25 Term: 0-22 >6 months: 0-5	No cell count result can exclude bacterial meningitis; PMN count typically in 1000s but may be less dramatic or even normal (classically, in very early meningococcal meningitis and in extremely ill neonates); lymphocytosis with normal CSF chemistries seen in 15-25%, especially when cell counts < 1000 or with partial treatment; ~90% of patients with ventriculoperitoneal shunts who have CSF WBC count >100 are infected; CSF glucose is usually normal, and organisms are less pathogenic; cell count and chemistries normalize slowly (over days) with antibiotics	Cell count usually < 500, nearly 100% mononuclear; up to 48 hours, significant PMN pleocytosis may be indistinguishable from early bacterial meningitis; this is particularly true with eastern equine encephalitis; presence of nontraumatic RBCs in 80% of HSV meningoencephalitis, though 10% have normal CSF results	Hundreds of mononuclear cells
Microscopy No organisms	Gram stain 80% sensitive; inadequate decolorization may mistake *Haemophilus influenzae* for gram-positive cocci; pretreatment with antibiotics may affect stain uptake, causing gram-positive organisms to appear gram-negative and decrease culture yield by average of 20%	No organism	India ink is 50% sensitive for fungi; cryptococcal antigen is 95% sensitive; AFB stain is 40% sensitive for tuberculosis (increase yield by staining supernatant from at least 5 mL CSF)
Glucose Euglycemia: >50% serum Hyperglycemia: >30% serum Wait 4 hr after glucose load	Decreased	Normal	Sometimes decreased; aside from fulminant bacterial meningitis, lowest levels of CSF glucose are seen in tuberculous meningitis, primary amebic meningoencephalitis, and neurocysticercosis
Protein (mg/dL) Preterm: 65-150 Term: 20-170 >6 months: 15-45	Usually >150, may be >1000	Mildly increased	Increased; >1000 with relatively benign clinical presentation suggestive of fungal disease

*Some bacteria (eg, *Mycoplasma*, *Listeria*, *Leptospira* spp, *Borrelia burgdorferi* [Lyme], and spirochetes) produce spinal fluid alterations that resemble the viral profile. An

aseptic profile also is typical of partially treated bacterial infections (>33% of patients have received antimicrobial treatment, especially children) and the 2 most common causes of encephalitis—the potentially curable HSV and arboviruses. **In contrast, tuberculous meningitis and parasites resemble the fungal profile more closely.

CFS sample handling

- Tube 1 – Send to the chemistry laboratory for glucose and protein
- Tube 2 – Send to the hematology laboratory for a cell count with differential
- Tube 3 – Send to the microbiology and immunology laboratory
- Tube 4 – Hold for a repeat cell count with differential, if needed (or for other subsequent studies not initially ordered)

Microbiology and immunology studies for tube 3 include the following:

- Gram stain
- Bacterial culture
- Acid-fast bacillus (AFB) stain and tuberculosis cultures
- India ink stain
- Cryptococcal antigen testing
- Fungal cultures, counterimmunoelectrophoresis (*CIE*), VDRL, and cryptococcal antigen, if indicated

Tumor necrosis factor alpha (TNF-α), interleukin (IL)-1, and other cytokines have received increasing attention as mediators of the inflammatory response during bacterial meningitis.[40]

Mustafa et al demonstrated that IL-1β can be detected in the CSF of 95% of infants and children with bacterial meningitis and that levels higher than 500 pg/mL were correlated with an increased risk of neurologic sequelae.[50]

These findings, though requiring both confirmation and amplification, suggest that analysis of TNF and other cytokines, in particular IL-1β, may prove valuable in differentiating acute bacterial meningitis from viral meningitis and possibly in detecting patients at particular risk for an adverse outcome. Their role in guiding adjunctive therapy, such as corticosteroids and nonsteroidal treatment of blood-brain barrier injury, is also under investigation.[40]

CSF characteristics of acute bacterial meningitis

Examination of the CSF in patients with acute bacterial meningitis reveals the characteristic neutrophilic pleocytosis (cell count usually ranging from hundreds to a few thousand, with >80% PMNs). In some (25-30%) cases of *L monocytogenes* meningitis, a lymphocytic predominance may occur. A low CSF white blood cell (WBC) count (< 20/µL) in the presence of a high bacterial load suggests a poor prognosis. According to Seupaul, the following 3 findings on CSF analysis have clinically useful likelihood ratios for the diagnosis of bacterial meningitis in adults:[51]

- CSF glucose−to−blood glucose ratio of 0.4 or lower.
- CSF WBC count of 500/µL or higher.
- CSF lactate level of 31.53 mg/dL or higher

CSF characteristics of viral meningitis

In viral meningitis, the opening pressure is 90-200 mm H_2 O, and the WBC count is 10-300/µL. Although the glucose concentration is typically normal, it can be below normal in meningitis from lymphocytic choriomeningitis virus (LCM), herpes simplex virus (HSV), mumps virus, and poliovirus. The protein concentration tends to be slightly elevated, but it can be within the reference range.[40]

CSF characteristics of fungal meningitis

The diagnosis of cryptococcal meningitis relies on the identification of the pathogen in the CSF. The CSF is characterized by a lymphocytic pleocytosis (10-200/µL), a reduced glucose level, and an elevated protein level. The CSF picture of other fungal meningitides is similar to that of cryptococcal meningitis, usually with lymphocytic pleocytosis. Eosinophilic pleocytosis has rarely been associated with *C immitis* meningitis. The definitive diagnosis usually relies on the demonstration of the specific fungal agent (eg, *H capsulatum, C immitis, B dermatitidis,* or *Candida* species) from clinical specimens, including the CSF. This could be in the form of fungal culture isolation (eg, *C albicans* growth from CSF). More commonly, fungal serology (eg, presence of histoplasma antigen in the CSF) is used in the diagnosis of many cases of fungal meningitis because isolating these organisms from culture has proved difficult. It should be noted, however, that the serology for *B dermatitidis* is not accurate and a negative serology finding does not rule out the diagnosis.[40]

CSF characteristics of eosinophilic/parasitic meningitis

Primary amebic meningoencephalitis (PAM) caused by *N fowleri* is characterized by a neutrophilic pleocytosis, low glucose levels, elevated protein levels, and red blood cells (RBCs). Mononuclear pleocytosis may be observed in patients with subacute or chronic forms of PAM. Demonstration of the trophozoites, with the characteristic ameboid movement, on wet preparations of the CSF has been used for diagnosis. Alternatively, the ameba may be demonstrated in biopsy specimens. In the presence of exposure, profound peripheral blood eosinophilia, and characteristic eosinophilic pleocytosis, suspicion of meningitis caused by *A cantonensis, G spinigerum,* or *B procyonis* should be entertained. Demonstrating the larvae ante mortem is usually difficult, and diagnosis relies on clinical presentation and a compatible epidemiologic history. Serologic tests may aid in the diagnosis. *G spinigerum* meningitis may mimic cerebrovascular disease in that it may cause cerebral hemorrhage.[40]

CSF characteristics of Lyme meningitis

In patients with Lyme meningitis, the CSF is characterized by low-grade lymphocytic pleocytosis, low glucose levels, and elevated protein levels. Oligoclonal bands reactive to *B burgdorferi* antigens may be present. Demonstration of the specific antibody to *B burgdorferi* aids in the diagnosis. Comparison between the antibody response in the CSF and that in the serum is a helpful diagnostic test. A CSF-to-serum ratio greater than 1 suggests intrathecal antibody production and neuroborreliosis.[40]

CSF characteristics of tuberculous meningitis

In patients with tuberculous meningitis, the CSF is characterized by a predominantly lymphocytic pleocytosis; an elevated protein level, especially if a CSF block is present; and a low glucose level (< 40 mg/dL). PCR testing can provide a rapid diagnosis, though false-negative results may occur in samples containing very few organisms (< 2 colony-forming units [cfu]/mL).[40]

CSF glucose and protein

In bacterial meningitis, the CSF glucose level (reference range, 40-70 mg/dL) is less than 40 mg/dL in 60% of patients. A simultaneous blood glucose determination should be obtained for the purposes of comparison. In patients with elevated blood glucose levels as a result of diabetes mellitus, the CSF-to-blood glucose ratio may not be predictive. The CSF glucose level is usually within the reference range in viral meningitis, but it may be low in some cases of LCM, HSV, mumps virus, or poliovirus infection. The CSF protein level (reference range, 20-50 mg/dL) is usually elevated in bacterial meningitis. In viral meningitis, these levels are also usually elevated, though they can be within the reference range. In syphilitic meningitis, abnormal CSF protein levels (elevated) and CSF glucose levels (decreased) may be observed in 10-70% of cases.[40]

CSF Gram stain and acid-fast bacillus stain

Gram staining of the CSF permits rapid identification of the bacterial cause in 60-90% of patients with bacterial meningitis. The presence of bacteria is 100% specific, but the sensitivity of this test for detection is variable. The

likelihood of detection is higher in the presence of a higher bacterial concentration and diminishes with prior antibiotic use. The demonstration of AFB (eg, with auramine-rhodamine stain, Ziehl-Neelsen stain, or Kinyoun stain) in the CSF is difficult and usually requires a large volume of CSF. Meningeal biopsy, with the demonstration of caseating granulomas and AFB on the smear, offers a higher yield than the CSF AFB smear.[40]

CSF culture and antigen testing

CSF bacterial cultures yield the bacterial cause in 70-85% of cases. The yield diminishes by 20% in patients who have received antimicrobial therapy. In these cases, some experts advocate the use of a CSF bacterial antigen assay. This is a latex agglutination technique that can detect the antigens of *H influenzae* type B (Hib), *S pneumoniae, N meningitidis, E coli* K1, and *S agalactiae* (group B streptococcus [GBS]). Its theoretical advantage is the detection of the bacterial antigens even after microbial killing, as is observed after antibacterial therapy.[40]

Another attractive alternative is using the Binax NOW for *S pneumoniae* in the CSF. This assay has a 99-100% sensitivity and specificity for ruling out the most common cause of bacterial meningitis.[48]

Others studies, however, have shown that the CSF bacterial antigen assay may not be better than the Gram stain. Although it is specific (a positive result indicates a diagnosis of bacterial meningitis), a negative finding on the bacterial antigen test does not rule out meningitis (50-95% sensitivity).

Cryptococcal meningitis

C neoformans may be cultured from the CSF in cryptococcal meningitis. Other methods of identification include India ink preparation and the detection of CSF cryptococcal antigen. India ink has a sensitivity of only 50%, but it is highly diagnostic if positive. Because of the low sensitivity of the India ink preparation, many centers have adapted the use of CSF cryptococcal antigen determination, a test with a sensitivity exceeding 90%. However, the CSF cryptococcal antigen determination is not universally available. In instances when the India ink results are negative but the degree of clinical suspicion for cryptococcal meningitis is high, the CSF specimen may be sent to reference laboratories that can perform CSF cryptococcal antigen determination to confirm the diagnosis. In addition, the titer of the antigen could serve to monitor the response to treatment. Blood cultures and serum cryptococcal antigen should be obtained to determine whether cryptococcal fungemia is present.[40]

Syphilitic meningitis

In syphilitic meningitis, isolating *T pallidum* from the CSF is extremely difficult and time-consuming. The spirochete could be demonstrated by using dark-field or phase-contrast microscopy on specimens collected from skin lesions (eg, chancres and other syphilitic lesions). The diagnosis is usually supported by the CSF VDRL test, which has a sensitivity of 30-70% (a negative result on the CSF VDRL test does not rule out syphilitic meningitis) and a high specificity (a positive test result suggests the disease). Care must always be taken not to

contaminate the CSF with blood during spinal fluid collection (eg, traumatic tap).[40]

Lyme meningitis

CSF culture for *B burgdorferi* has a low yield. The CSF Lyme PCR assay, if available, offers a rapid, sensitive, and specific method of diagnosis. This assay is gaining popularity as the method of choice for diagnosing Lyme meningitis.[40]

Cohn et al validated a clinical prediction rule for differentiating Lyme meningitis from aseptic meningitis. Their "rule of 7s" classifies children at low risk for Lyme meningitis when all of the following 3 criteria are met:[52]

- < 7 days of headache.
- < 70% CSF mononuclear cells
- Absence of cranial nerve VII palsy or other cranial nerve palsy

Tuberculous meningitis

Culture for *Mycobacterium* usually takes several weeks and may delay definitive diagnosis. *M tuberculosis* detection assays involving nucleic acid amplification have become available and have the advantages of rapidity, high sensitivity, and high specificity. There remains a need for mycobacterial growth in cultures because this method offers the advantage of performing drug susceptibility assays.[40]

Viral isolation from CSF

Isolation of viruses from the CSF has a sensitivity of 65-70% for enteroviruses. Alternatively, isolation of enteroviruses from throat and stool viral cultures may also indirectly implicate enterovirus as the cause of the meningitis. Culture of mumps virus from the CSF has a low sensitivity (30-50%). LCM virus may be cultured in blood early in the disease or in urine at a later stage.[40]

Radio imaging

Magnetic resonance imaging (MRI)

Diffuse meningeal enhancement is often seen after the administration of gadolinium. MRI may also show abscesses, tuberculomas, venous occlusions and adjacent infarctions.[53]

Computed tomography (CT)

Meningeal enhancement may be seen after contrast administration. CT may also show abscesses, tuberculomas, venous occlusions and adjacent infarctions. CT is particularly useful in detecting lesions that erode the skull such as a sinus wall defect.[54]

Other Tests

- Detection of tuberculostearic acid in cerebrospinal fluid gives a sensitive and rapid diagnosis of tuberculous meningitis.[55]

- Bromide partition test: The partition of bromide ion between serum and CSF after a loading dose reflects the integrity of the blood-brain barrier.

Serum/CSF bromide ratio (in simultaneous samples) less than 1.6 is found to be characteristic of tuberculous meningitis.[56]

- Estimation of free sialic acid and lactic acid in CSF: The contents of the acids are significantly higher in cases of pyogenic meningitis.[57,58]

- Estimation of Adenosine deaminase in CSF: The levels of this enzyme are significantly raised in CSF of patients with tuberculous meningitis.[59,60]

Chapter 4

Methodology

METHODOLOGY

The present one year cross sectional study was carried out in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Study design

The study design was a one year cross sectional study.

Study period and duration

The present one year study was conducted from January 2012 to December 2012.

Place

The present study was conducted at Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum a teaching hospital attached to Jawaharlal Nehru Medical College, Belgaum.

Source of Data

Patients presenting with meningitis at Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the study period were included in the study.

Sample size

A total of 50 patients presenting with meningitis were selected for the study.

Sampling procedure

The sample size was calculated using the following formula.

$n = 4 p q / d^2$

Where, p = Prevalence (50%)

q = 100 – p = 50%

d = Absolute error considered as 14%

Hence,

$n = 4 \times 50 \times 50 / 196^2$

$n = 51.02 \approx 50$

Selection criteria

Inclusion

- Patients presenting with signs of meningitis.
- Age more than 18 years.

Exclusion

- Patient with
    - Prior antibiotic therapy.
    - Head injury with meningitis.
    - Subarachnoid haemorrhage.

Ethical clearance

The ethical clearance was obtained from Institutional Ethics Committee, Jawaharlal Nehru Medical College, Belgaum.

Informed Consent

The patients fulfilling selection criteria were explained about the nature of the study. Those willing to participate were enrolled in the study after obtaining a written informed consent (Annexure I).

Method of collection of data

Patients were interviewed and demographic data such as age, sex and history pertaining to the other comorbid conditions was obtained. Further these patients were subjected to a thorough physical examination for vitals (pulse rate, blood pressure and respiratory rate) and other clinical signs and symptoms. The systemic examination was carried out. These findings were recorded on a predesigned and pretested proforma (Annexure II).

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

Investigations

CSF evaluation was done by lumbar puncture using 20 or 22 G spinal needle at admission. Further the detailed CSF analysis was carried out for;

- Protein.
- Sugar.
- ADA levels.
- Cell count
- Cell type.
- Gram's stain
- Acid fast bacilli (AFB)
- India-ink.
- Culture.

Blood

- Complete blood count.
- Haematocrit
- Renal function
- Liver function
- Arterial blood gas
- Serum electrolytes
- Electrocardigram
- Radiological studies
    - Chest X-ray

- Neuroimaging

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

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

Clinical

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

Laboratory

CSF Examination

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

Neuroimaging

- Diffuse meningeal enhancement on CT / MRI.

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

Group I (Tuberculous meningitis)

1. Clinical
    a. Usually insidious in onset.
    b. May be associated with tuberculosis (TB) of other organs for example pulmonary tuberculosis, TB lymphadenitis, abdominal tuberculosis.
    c. Signs of meningeal irritation.
2. Laboratory
    a. CSF analysis
        i. Pleocytosis of more than 10 cells per cubic millimeter, predominantly lymphocytes.
        ii. Proteins more than 45 mg/dL.
        iii. Sugar less than 40 mg/dL or less than 40% of the blood glucose concentration.
        iv. Ziehl – Neelsen (Z-N) stain may be positive for acid fast bacilli.
        v. Positive culture for AFB

vi. ADA more than 10 U/L.

b. Neuroimaging: May show meningeal enhancement, basal exudates and / or tuberculoma.

Group II (Pyogenic meningitis)

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

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

Group III (Viral Meningitis)

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

2. Laboratory
    a. CSF analysis
        i. Pleocytosis of more than 10 cells per cubic millimeter, predominantly lymphocytes.
        ii. Proteins more than 45 mg/dL.
        iii. Sugar normal.
        iv. PCR may be positive for the DNA or RNA of the causative virus.
    b. Neuroimaging: May show diffuse meningeal enhancement.

Group IV (Toxoplasma meningitis)

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

2. Laboratory
    a. CSF Analysis

i. Pleocytosis of more than 10 cells per cubic millimeter, predominantly mononuclear cells.
ii. Proteins more than 45 mg/dl.
iii. Sugar normal or decreased.
iv. CSF sediment may show the organisms.
v. Immunoglobulin M indirect fluorescent antibody titre may be positive.

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

Group V (Cryptococcal meningitis)

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

2. Laboratory
    a. CSF analysis
        i. Variable pleocytosis, predominantly lymphocytic.
        ii. Proteins more than 45 mg/dL.
        iii. Sugar less than 40 mg/dl or less than 40% of the blood glucose concentration.
        iv. India ink preparation is distinctive and diagnostic.

v. Latex agglutination test for the cryptococcal polysaccharide antigen gives rapid results.

vi. The organism may be grown in fungal cultures.

b. Neuroimaging: May show diffuse meningeal enhancement or a solitary cryptococcoma.

Statistical analysis

The data obtained was coded and entered into Microsoft Excel Worksheet (Annexure III). The categorical data was expressed as rates, ratios and proportions and comparison was done using chi-square test. The continuous data was expressed as mean ± standard deviation (SD) and comparison was done by two sample 't' test with unequal variance. Comparison of three or more mean values was done using one way ANOVA test. A probability value ('p' value) of less than or equal to 0.05 was considered as statistically significant.

Chapter 5

Results

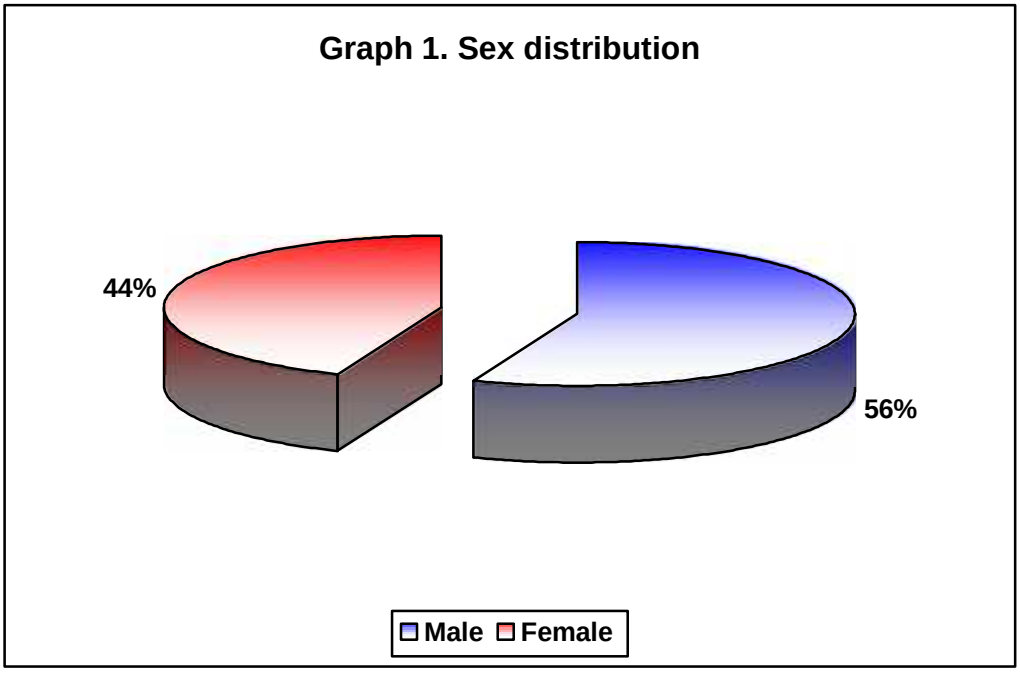
RESULTS

This one year cross-sectional study was carried out in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 50 patients presenting with meningitis aged more than 18 years were studied.

The data obtained was coded and entered into the Microsoft excel and the data was analysed. The final results and interpretations were tabulated as below.

Table 1. Sex distribution

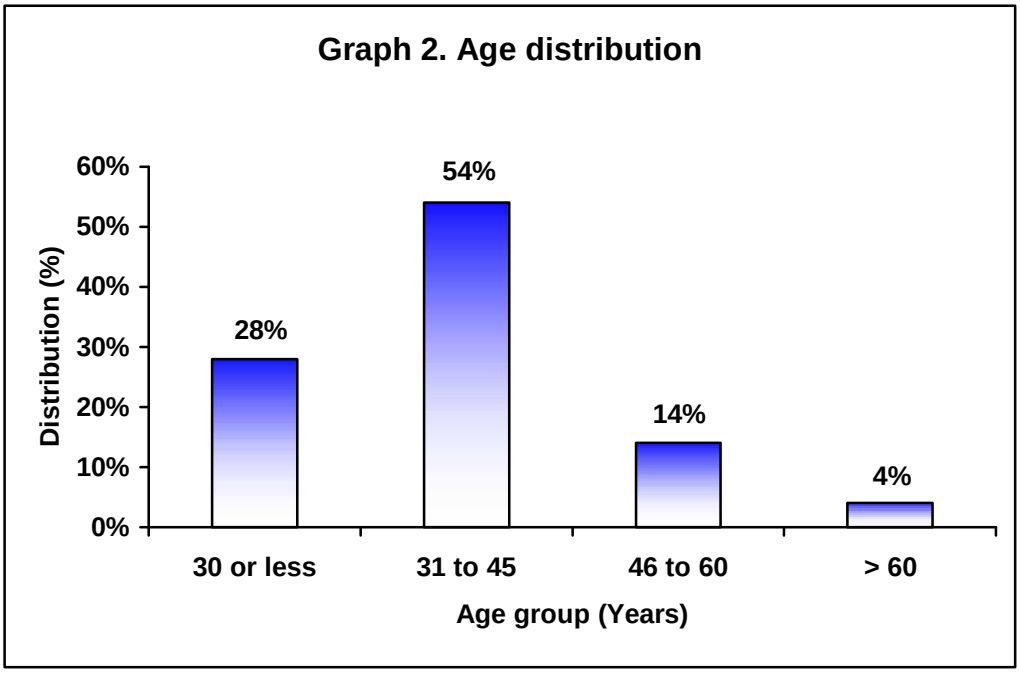
Sex	Distribution (n=50)	
	Number	**Percentage**
Male	28	56.00
Female	22	44.00
Total	**50**	**100.00**



In the present study 56% were males and 44% were females. The male to female ratio was 1.2:1.

Table 2. Age distribution

Age group (Years)	Distribution (n=50)	
	Number	**Percentage**
30 or less	14	28.00
31 to 45	27	54.00
46 to 60	7	14.00
> 60	2	4.00
Total	**50**	**100.00**

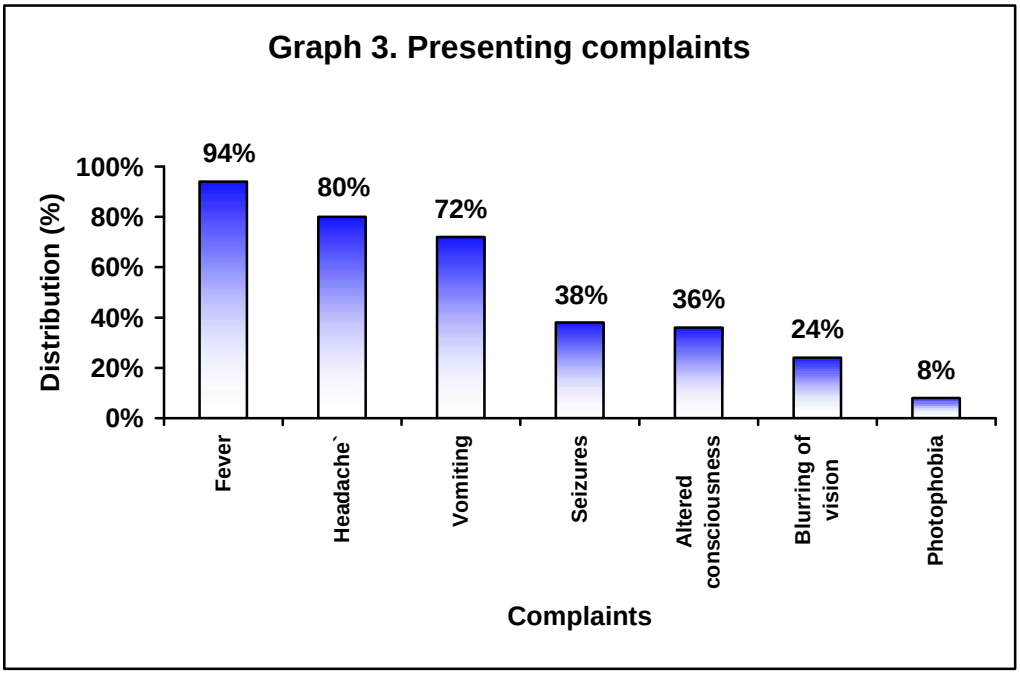


In this study 54% of the patients were aged between 31 to 45 years and 28% were aged ≤ 30 years. 14% were aged between 46 to 60 years and 4% were aged above 60 years. The mean age was 36.10 ± 13.21 years.

Table 3. Presenting complaints

Complaints	Distribution (n=50)	
	Number	Percentage
Fever	47	94.00
Headache	40	80.00
Vomiting	36	72.00
Seizures	19	38.00
Altered consciousness	18	36.00
Blurring of vision	12	24.00
Photophobia	4	8.00

Multiple findings present hence total not shown



In this study the commonest presentation was fever (94%) followed by headache (80%), vomiting (72%), seizures (38%), altered sensorium (36%), blurring of vision (24%), and photophobia (8%).

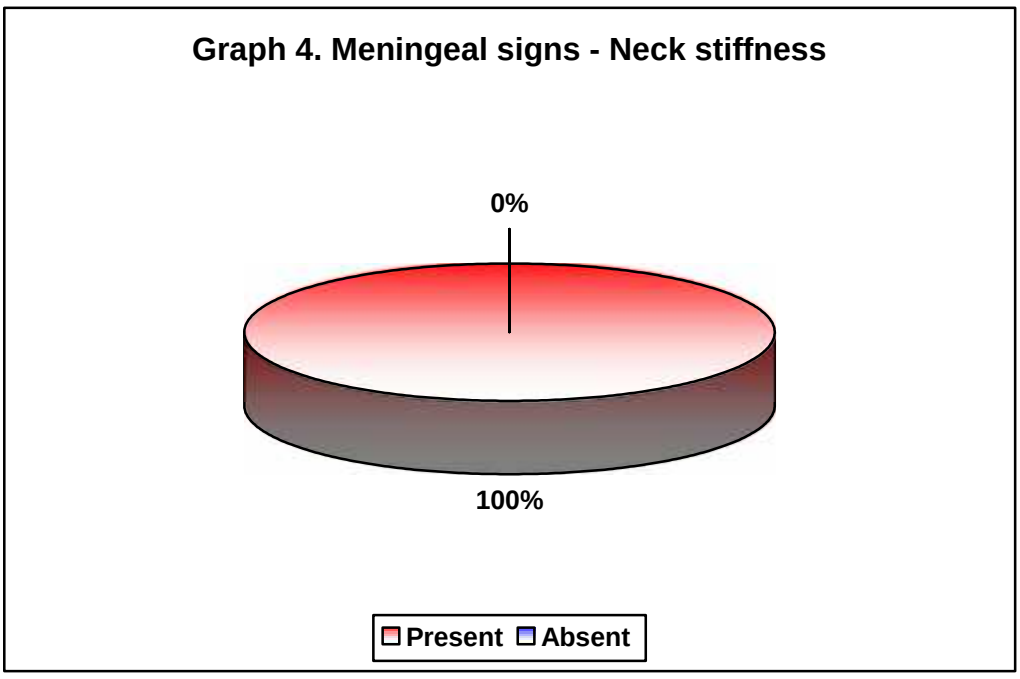
Table 4. Central nervous system examination

Findings	Distribution (n=50)	
	Number	**Percentage**
Signs of meningeal irritation	50	100.00
Altered consciousness	18	36.00
Cerebellar signs	13	26.00
Motor deficits	00	0.00
Sensory deficit	00	0.00
Cranial nerve palsy	00	0.00

In this study signs of meningeal irritation were present in all the patients (100%). Altered consciousness and cerebellar signs were present in 36% and 26% of patients respectively.

Table 5. Meningeal signs - Neck stiffness

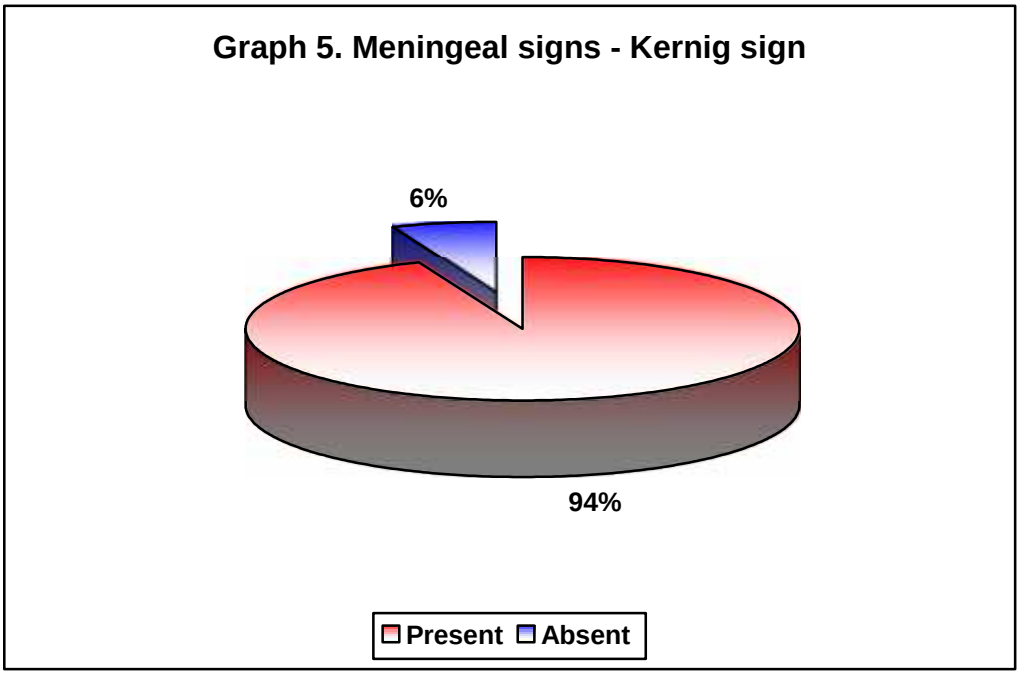
Findings	Distribution (n=50)	
	Number	**Percentage**
Present	50	100.00
Absent	0	0.00
Total	**50**	**100.00**



In the present study neck stiffness was present in all the patients (100%).

Table 6. Meningeal signs - Kernig sign

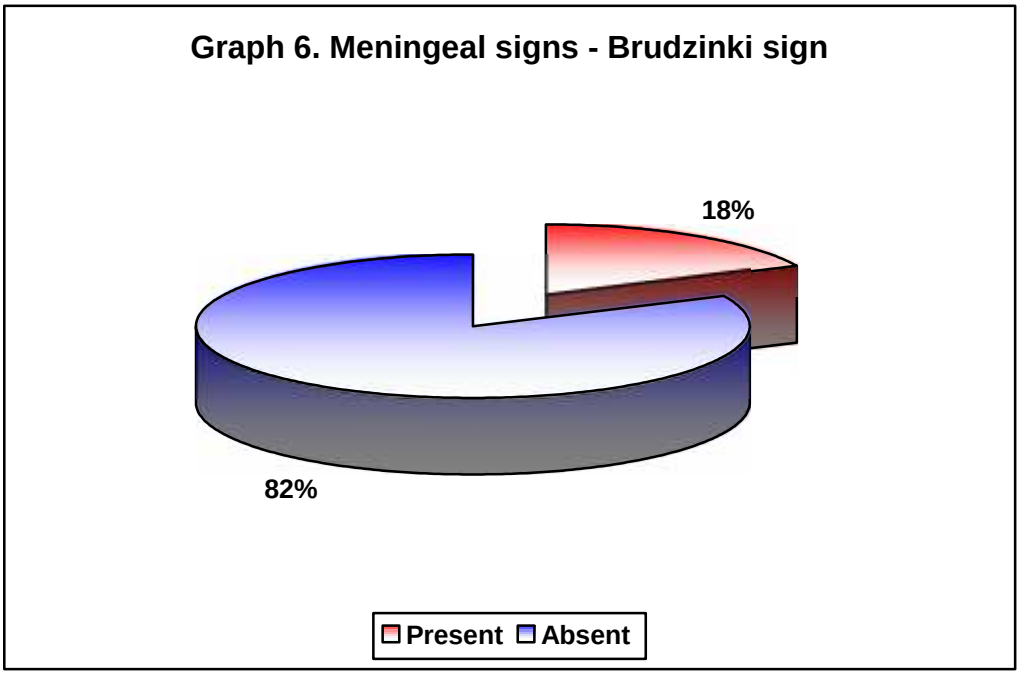
Findings	Distribution (n=50)	
	Number	**Percentage**
Present	47	94.00
Absent	3	6.00
Total	**50**	**100.00**



In the present study, Kernig sign was noted among 94% of patients.

Table 7. Meningeal signs - Brudzinki sign

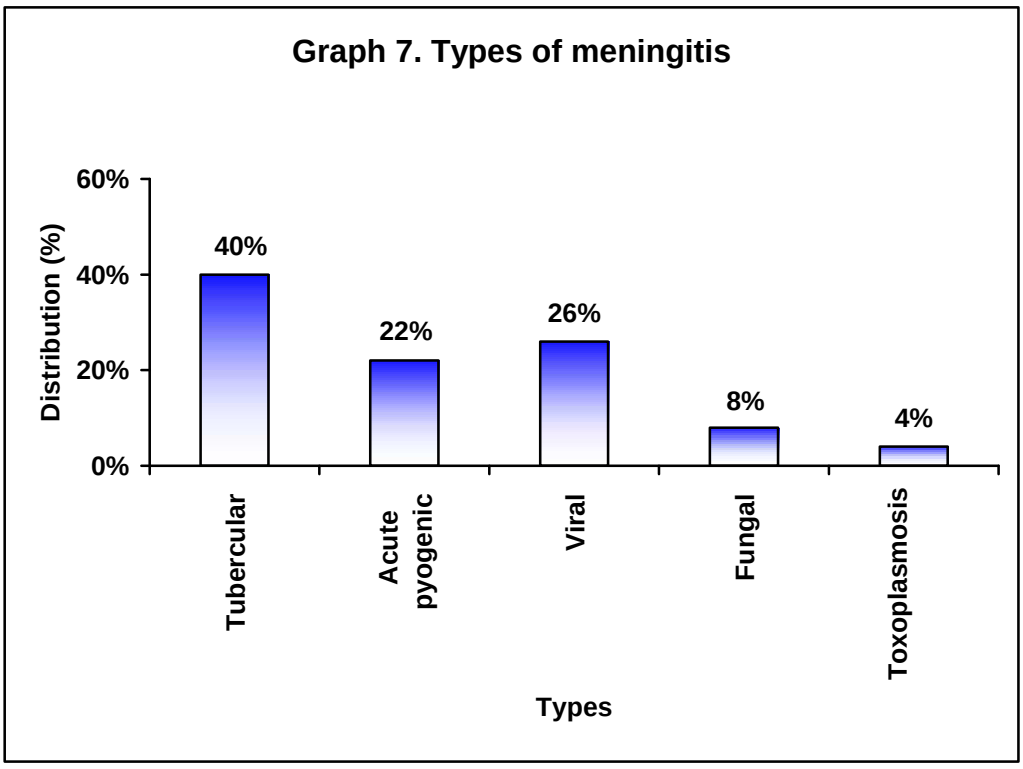
Findings	Distribution (n=50)	
	Number	**Percentage**
Present	9	18.00
Absent	41	82.00
Total	**50**	**100.00**



In the present study, Brudzinki sign was present in 18% of the patients.

Table 8. Types of meningitis

Types	Distribution (n=50)	
	Number	**Percentage**
Tubercular	20	40.00
Acute pyogenic (Bacterial)	11	22.00
Viral	13	26.00
Fungal (Cryptococcus)	4	8.00
Toxoplasmosis	2	4.00
Total	**50**	**100.00**



In the present study 40% of the patients had tubercular meningitis and 26% of the patients had viral meningitis. In the remaining acute pyogenic meningitis was present in 22%, fungal in 8% and toxoplasmosis in 4%.

Table 9. Mean CSF cortisol levels in different types of meningitis

Types	Distribution (n=50)	
	Mean	**SD**
Tubercular	34.50	8.45
Acute pyogenic (Bacterial)	25.00	6.99
Viral	16.00	7.93
Fungal (Cryptococcus)	20.00	4.32
Toxoplasmosis	25.50	3.54

F=5.219

p=0.001

In this study the mean CSF cortisol levels were high in patients with tubercular meningitis (34.50 ± 8.45) compared to toxoplasmosis (25.50 ± 3.54), Acute pyogenic (Bacterial) (25.00 ± 6.99), fungal (20.00 ± 4.32) and viral (16.00 ± 7.93). This difference was statistically significant ($p<0.001$).

Table 10. Comparison of CSF cortisol level in bacterial and viral meningitis

Menigitis	CSF cortisol				Total (n=44)	
	Elevated		Normal			
	No	%	No	%	No	%
Acute pyogenic (Bacterial)	23	74.19	8	25.81	31	100.00
Viral	4	30.77	9	69.23	13	100.00
Total	**27**	**61.36**	**17**	**38.64**	**44**	**100.00**

p = 0.007

In the present study, of the 31 patients with bacterial meningitis, 74.19% had elevated CSF cortisol compared 25.81% with normal CSF cortisol. This difference was statistically significant (p=0.007).

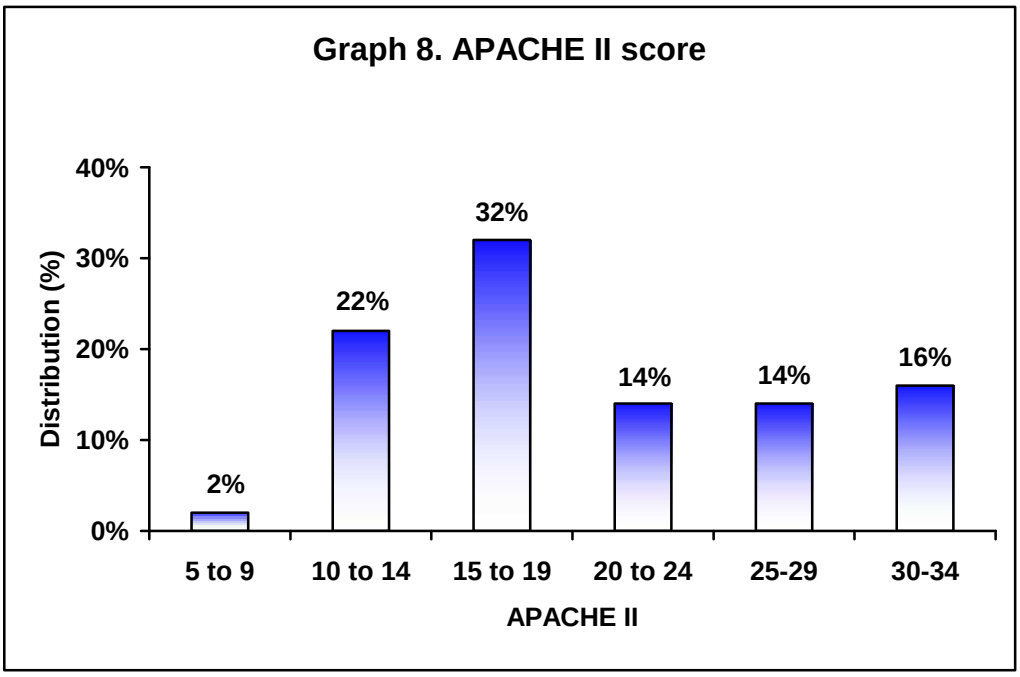
Table 11. Comparison of CSF cortisol level in different types of meningitis

Meningitis	CSF cortisol				Total (n=44)	
	Elevated		Normal			
	No	%	No	%	No	%
Bacterial	8	72.73	3	27.27	11	100.00
Tubercular	15	75.00	5	25.00	20	100.00
Viral	9	69.23	4	30.77	13	100.00
Fungal	1	25.00	3	75.00	4	100.00
Toxoplasmosis	2	100.00	0	0.00	2	100.00
Total	**35**	**70.00**	**15**	**30.00**	**50**	**100.00**

In the present study, of the 20 patients with tubercular meningitis, 75% had elevated CSF cortisol levels compared 25% with normal.

Table 12. APACHE II score

APACHE II	Distribution (n=50)	
	Number	**Percentage**
5 to 9	1	2.00
10 to 14	11	22.00
15-19	16	32.00
20-24	7	14.00
25-29	7	14.00
30 to 34	8	16.00
Total	**50**	**100.00**



In this study 32% of the patients had APACHE II scores between 15 to 19. The distribution of other patients is as shown in table 10 and graph 10.

Table 13. APACHE II Score and CSF Cortisol levels

APACHE II score	CSF cortisol				Total	
	Elevated		Normal			
	No	%	No	%	No	%
5 to 9	0	0.00	1	100.00	1	100.00
10 to 14	5	45.45	6	54.55	11	100.00
15-19	7	43.75	9	56.25	16	100.00
20-24	3	42.86	4	57.14	7	100.00
25-29	7	100.00	0	0.00	7	100.00
30-34	8	100.00	0	0.00	8	100.00
Total	**30**	**60.00**	**20**	**40.00**	**50**	**100.00**

p=0.041

In this study of the 8 and 7 patients with APACHE II score between 30 to 34 and 25 to 29, all (100%) the patients had raised CSF cortisol levels whereas in 11 patients with APACHE II score between 10 to 14, 54.55% of patients had normal CSF cortisol levels. This difference was statistically significant (p=0.041).

Chapter 6

Discussion

DISCUSSION

Meningitis is an inflammation of the protective membranes covering the brain and spinal cord, collectively known as the meninges.[61] It can lead to serious long-term consequences such as, deafness, epilepsy, hydrocephalus and cognitive deficits especially if not treated quickly.[62]

The term aseptic meningitis refers loosely to all cases of meningitis in which no bacterial infection can be demonstrated. 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 and hospital admissions.[63]

The most important test in identifying or ruling out meningitis is analysis of the cerebrospinal.[64] Use of various biological markers in blood (C-reactive protein, white blood cell count and procalcitonin) or cerebrospinal fluid (protein, glucose, cell count, cell type, gram stain, AFB, India ink, ADA, culture, lactate dehydrogenase and inflammatory cytokines) or combinations of them has been suggested to improve sensitivity in determining the etiological diagnosis.[65]

Increased CSF cortisol levels have previously been reported in various CNS disorders such as, multiple sclerosis, Alzheimer's disease, depression and post-traumatic stress disorder,[66] however, the CSF cortisol concentrations were much higher in patients with bacterial meningitis.[67] The present study was planned to estimate CSF cortisol levels as a marker to differentiate the types of meningitis and to correlate CSF cortisol levels with severity.

This one year cross-sectional study was carried out in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 50 patients presenting with meningitis aged more than 18 years were studied.

In the present study The male to female ratio was 1.2:1. Male preponderance was noted, 56% were males and 44% were females. Similar findings were reported in a study by Holub M. et al where the meningitis was noted in 61.7% of males and in females was 38.3%.[67]

In this study peak incidence of meningitis was seen in the age group of 31 to 45 years (54%) followed by ≤ 30 years (28%) and the mean age was 36.10 ± 13.21 years. Holub M et al observed the mean age of 42 years in his study.[67]

In this study the commonest presentation was fever (94%) followed by headache (80%) and vomiting (72%). However the other presentations were seizures (38%), altered sensorium (36%), blurring of vision (24%), and photophobia (8%).

In the present study, classical signs of meningeal irritation that is neck stiffness was present in all the patients (100%) while Kernig sign and Brudzinki sign were noted among 94% and 18% of the patients respectively. Other signs like altered consciousness and cerebellar signs were present in 36% and 26% of patients respectively. A study by Van de Beek D et al[68] reported the classic triad of fever, neck stiffness and change in mental status in 44% of cases, however 95% had atleast two of the four symptoms of headache, fever, neck stiffness and

altered mental status and the incidence of seizures was 17%. Khatua et al,[69] reported neck rigidity in 54% cases and Kernig's sign in 40% of cases.

In this study 40% of the patients had tubercular meningitis and 26% of the patients had viral meningitis. In the remaining acute pyogenic meningitis was present in 22%, fungal in 8% and toxoplasmosis in 4%. The mean CSF cortisol levels were high in patients with tubercular meningitis (34.50 ± 8.45) compared to toxoplasmosis (25.50 ± 3.54), Acute pyogenic (Bacterial) (25.00 ± 6.99), fungal (20.00 ± 4.32) and viral (16.00 ± 7.93). This difference was statistically significant ($p<0.001$). Further analysis of the 31 patients with bacterial meningitis showed, 74.19% had elevated CSF cortisol and 25.81% with normal CSF cortisol. In 13 patients with viral meningitis 30.77% of patients showed elevated CSF cortisol and 69.23% showed normal CSF cortisol levels. This difference was statistically significant ($p=0.007$). These findings suggest strong association between elevation in CSF cortisol levels and bacterial meningitis. Holub H et al[67] in his comparative study also reported CSF cortisol concentrations were significantly elevated in patients with bacterial meningitis as compared with concentrations in patients with aseptic meningitis as well as in healthy control individuals. A study by Singhi SC et al[70] also reported the mean serum cortisol levels were significantly higher in bacterial meningitis compared to aseptic meningitis.

van Woensel and coworkers[71] reported higher concentrations in patients with meningococcal meningitis than in those with fulminant meningococcal sepsis, which is the most severe form of invasive meningococcal disease. However, the CSF cortisol concentrations were much higher in patients with

bacterial meningitis. These differences are most likely due to the severity of bacterial meningitis, which is associated with systemic inflammation, intense stress response and compromised blood-brain barrier.[72]

In this study 2% patients had APACHE II score between 5 to 9, 22% of patients had APACHE II score between 10 to 14, 32% of patients had APACHE II score between 15 to 19, 14% patients had APACHE II score between 22 to 24, other 14% patients had APACHE II score between 25 to 29, 16% patients had APACHE II score between 32 to 34.

In present study we have observed patients with APACHE II score between 25 to 34 all had elevated CSF cortisols. Patients with APACHE II score of 22 to 24, 15 to 19 and 10 to 14 showed elevated CSF cortisol in 42.86%, 43.75% and 45.45% respectively. Patients with APACHE II score 5 to 9 had normal CSF cortisol this difference was statistically significant (p=0.041). High CSF cortisol levels correlated with APACHE II score. Holub M et al[67] also found strong correlations between high CSF cortisol and elevated APACHE II, scores in the 47 patients with acute bacterial meningitis.

This study has certain limitations viz. smaller sample size which limited us to find the association between CSF cortisol levels and other types of meningitis. Further studies on large sample with standardized meningitis patients with equal distribution of types of meningitis along with healthy controls would further provide insights in the role CSF cortisol among the patients with meningitis.

Chapter 7

Conclusion

CONCLUSION

In this study 40% of the patients had tubercular meningitis, 26% had viral meningitis, 22% had pyogenic meningitis, fungal in 8% and toxoplasmosis in 4% of the patients. The mean CSF cortisol levels were significantly high in patients with tubercular meningitis (34.50 ± 8.45) compared to toxoplasmosis (25.50 ± 3.54), acute pyogenic (Bacterial) (25.00 ± 6.99), fungal (20.00 ± 4.32) and viral (16.00 ± 7.93). Furthermore, bacterial meningitis showed significantly higher number of patients with elevated CSF cortisol and APACHE II scores.

Chapter 8

Summary

SUMMARY

Increased CSF cortisol levels have previously been reported in various CNS disorders. The present study was planned to estimate CSF cortisol levels as a marker to differentiate the types of meningitis and to correlate CSF cortisol levels with severity.

This one year cross-sectional study was carried out in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 50 patients presenting with meningitis aged more than 18 years were studied.

In the present study 56% were males and 44% were females with male to female ratio of 1.2:1. The commonest age group was 31 to 45 years with 54% of the patients and the mean age was 36.10 ± 13.21 years. The commonest presentation was fever (94%) followed by headache (80%) and vomiting (72%). Signs of meningeal irritation were present in all the patients (100%). Altered consciousness and cerebellar signs were present in 36% and 26% of patients respectively. Neck stiffness was present in all the patients (100%) while Kernig and Brudzinki sign was noted among 94% and 18% of the patients. 40% of the patients had tubercular meningitis and 26% of the patients had viral meningitis. In the remaining acute pyogenic meningitis was present in 22%, fungal in 8% and toxoplasmosis in 4%.

In this study the mean CSF cortisol levels were high in patients with tubercular meningitis (34.50 ± 8.45) compared to toxoplasmosis (25.50 ± 3.54), Acute pyogenic (Bacterial) (25.00 ± 6.99), fungal (20.00 ± 4.32) and viral (16.00

± 7.93). This difference was statistically significant ($p<0.001$). Of the 31 patients with bacterial meningitis, 74.19% had elevated CSF cortisol ($p=0.007$). Patients with APACHE II score between 25 to 35, all (100%) patients had raised CSF cortisol levels ($p=0.041$). Out of 13 patients, 30.77% patients of viral meningitis had elevated CSF cortisol.

Chapter 9

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Annexures

Annexure I

ANNEXURE I – CONSENT FORM

"ESTIMATION OF CSF CORTISOL LEVELS IN PATIENTS WITH MENINGITIS - A ONE YEAR CROSS-SECTIONAL STUDY"

Objective and purpose of the study:

. This research is intended to estimate the CSF cortisol levels in patients with Meningitis. The principal investigator of the study is Dr. **** ******* under the guidance of Dr. **** ******.

Procedure:

If you agree to be part of the research study you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood sample and get a chest x ray/ECG,CT-SCAN,MRI SCAN (if required) done for the same study. You will have to undergo Lumbar Puncture for CSF fluid analysis

Risk and Benefits:

The only risk and possible discomfort you might get is while taking blood from your arm for the investigations. It may cause swelling, pain, redness, bruising or infection (rarely happens) at the site from where the blood is drawn.

You may also face some radiation hazards while getting an x ray done.

You may also have risks due to lumbar puncture which include Post-spinal headache & nausea, Spinal or epidural bleeding, trauma to spinal cord or nerve roots which can cause paraplegia, and epidural haemorrhage.

Alternatives

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part you can later change my mind and

withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsorer may stop your participation in this study any time. If you choose not to take part in the study you will receive the standard treatment for patients with your condition.

VOLUNTARY PARTICIPATION/ WITHDRAWAL:

Your participation in this study is entirely voluntary and you may withdraw from the study at any time.

Privacy and Confidentiality

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy

Does not apply to this research

Financial incentives for participation

You will not be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

If you have any questions about my rights as a participant you may call Dr. ******* ******, Principal and Chairman, J.N.M.C Ethical Committee for Human Research phone number **** *******.

CONSENT FORM

I voluntarily agree to take part in this study by signing on the line below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicated that I have read this entire consent form or it has been read to me, and has been explained to me in my vernacular language and had all my questions answered. I will be given a copy of this consent form.

Signature /Left Thumb print of the Participant or legally authorized representative.

Participant's Name/ : …….

Signature/ Left Thumb

Impression of the participant's : …….

Name of the legally

authorized representative/ Guardian : …….

Signature/ Left Thumb Impression. : …….

Witness's Name : …….

Signature/ Left Thumb Impression. :…….

Investigators name and Signature : …….

Date and Place : …….

Dr. **** ******
Professor,
Dept. of Medicine, J. N. Medical College,
K.L.E. University, Belgaum 10.
Ph.No. ***** *******
Ext. ****

Dr. ***** *******
Post-Graduate,
Department of Medicine,
J.N. Medical College,
Belgaum
Ph.No. **** ******
Ext. *****

Annexures

Annexure II

ANNEXURE II – PROFORMA

Patient Name: I.P number:

Age: Sex:

Address: Occupation:

Date of admission: Date of discharge:

SYMPTOMS:

1. Fever Yes/No
2. Headcahe Yes/No
3. Vomiting Yes/No
4. Altered consciousness Yes/No
5. Blurring of vision Yes/No
6. Photophobia Yes/No
7. Seizures Yes/No
8. Symptoms suggestive of neuro deficit Yes/No

PAST HISTORY:

1.Meningitis Yes/No

2.Trauma, Surgeryon head Yes/No

TREATMENT HISTORY:

Steroid therapy Yes/No

Chronic Antibiotic use Yes/No

PERSONAL HISTORY:

Habits: h/o smoking and tobbacco consumption Yes/No

H/o Alcohol consumption Yes/No

PHYSICAL EXAMINATION:

GENERAL CONDITION:

Level of Consciousness

Pallor: Yes/No

Icterus: Yes/No

Lymphadenopathy: Yes/No

Cyanosis: Yes/No

Clubbing: Yes/No

Edema: Yes/No

VITALS:

Temperature:

Pulse:

Respiratory rate:

Blood pressure:

SYSTEMIC EXAMINATION:

C.N.S:

C.V.S.:

P.A.:

R.S:

Investigation

APACHE II Score

CSF cortisol levels

Characteristics of CSF cortisol

Annexures

Annexure III

ANNEXURE IV – KEY TO MASTER CHART

-	-	Absent
+	-	Present
ABG	-	Arterial blood gas
ADA	-	Adenosine deaminase
APACHE	-	Acute physiology and chronic health evaluation
BP	-	Blood pressure
bpm	-	Beats per minute
CNS	-	Central nervous system
COPD	-	Chronic obstructive pulmonary disease
Crept	-	Creptococcal
CSF	-	Cerebrospinal fluid
CT	-	Computed tomography
dL	-	Deciliter
F	-	Female
gm	-	Gram
IMP	-	Impaired
M	-	Male
meq	-	Milli equivalent
mg	-	Milligram
mm	-	Millimeter
mm Hg	-	Millimeters of mercury
MRI	-	Magnetic resonance imaging
N	-	Normal

PaCO2	-	Arterial carbon dioxide tension
PaO2	-	Partial pressure of oxygen
T	-	Toxoplasmosis
WBC	-	White blood cell
ZN	-	Zeihl Neelsen