“ESTIMATION OF CSF LACTATE AS DIAGNOSTIC MARKER TO DIFFERENTIATE PYOGENIC MENINGITIS FROM NON-PYOGENIC MENINGITIS”

By

REG NO. BG0114012

Dissertation

Submitted to the
KLE University, Belagavi, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.
in
GENERAL MEDICINE

**DEPARTMENT OF GENERAL MEDICINE,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
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ENDORSEMENT

This is to certify that the dissertation entitled **"ESTIMATION OF CSF LACTATE AS DIAGNOSTIC MARKER TO DIFFERENTIATE PYOGENIC MENINGITIS FROM NON-PYOGENIC MENINGITIS"** is a bonafide research work done by CANDIDATE REG **NO. BG0114012**.

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LIST OF ABBREVIATIONS USED

ADA	-	Adenosine deaminase activity
AFB	-	Acid fast bacilli
AIDS	-	Acquired immune deficiency syndrome
ANOVA	-	Analysis of variance
BC	-	Before Christ
BM	-	Bacterial meningitis
CBC	-	Complete blood count
cells/m^3	-	Cells per cubic meter
CIDP	-	Chronic inflammatory demyelinating polyneuropathy
CNS	-	Central Nervous System
COX	-	Cyclooxygenase
CRP	-	C-reactive protein
CSF	-	Cerebrospinal fluid
CT	-	Computed tomography
EBV	-	Epstein Barr virus
eg,	-	For example,
ESR	-	Erythrocyte sedimentation rate
EVD	-	External ventricular derivation
FTA	-	Fluorescent treponemal antibody
g	-	grams
GB	-	Guillain-Barre
GBS	-	Group B streptococcus
GI	-	Gastrointestinal
HIV	-	Human immunodeficiency virus

HSV	-	Herpes simplex virus
ICP	-	Increased intracranial pressure
ie,	-	That is,
IgE	-	Immunoglobulin E
IL	-	Interleukin
LFT	-	Liver function test
mg/dL	-	Milligram per deciliter
mg/kg	-	Milligrams per kilogram
microL	-	Microlitre
mm Hg	-	Millimeters of mercury
mm	-	Millimeters
mmol/L	-	MIllimole per liter
MRC	-	Medical Research Council
MRI	-	Magnetic resonance imaging
MyD88	-	Myeloid differentiation 88
n	-	Total number
p	-	Probability value
PAF	-	Platelet activation factor
PCR	-	Polymerase chain reaction
PGE2	-	Prostaglandin e
PMNs	-	Polymorphonuclear leukocytes
RBS	-	Random blood sugar
RFT	-	Renal function test
SD	-	Standard deviation
TB	-	Tuberculosis

TBM	-	Tuberculer meningitis
TC	-	Total count
TLC	-	Total leukocyte count
TLRs	-	Toll-like receptors
TNF-α	-	Tumor necrosis factor alpha
UAE	-	United arab emirates
VRDL	-	Venereal disease research laboratory
VZV	-	Vericella Zoster virus
WBC	-	White blood cell
ZN	-	Ziehl-Neelsen

ABSTRACT

Background and objectives

Making a differential diagnosis between bacterial meningitis, aseptic meningitis and tubercular meningitis is a critical clinical problem. This study was planned to estimate CSF lactate as diagnostic marker to differentiate pyogenic meningitis from non-pyogenic Meningitis so as to evaluate its accuracy.

Methodology

This one year cross-sectional study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2015 to December 2015. A total of 70 patients presenting with meningitis aged more than 18 years were studied.

Results

Most of the patients were males (68.57%) and male to female ratio was 2:1. Most of the patients were aged between 18 to 40 years (42.85%) followed by 41 to 60 years (32.86%) and > 60 years (24.29%). The mean age was 46.51 ± 18.90 years. Most common clinical presentation was fever noted in 97.14%. Most of the patients has tubercular meningitis (42.86%) followed by viral (37.14%), pyogenic (15.71%) and cryptococcal (4.29%). Majority of the patients had CSF lactate levels of ≤5 mmol/L (78.57%) while lactate levels of 6 to 10 mmol/L, 11 to 15mmol/L and 15 to 20 mmol/L were noted in 8.57%, 8.57% and 4.29% of the patients respectively. The mean CSF lactate levels were 4.66 ± 4.07 mmol/L and median levels were 2.70 mmol/L with range 1 mmol/L being minimum and 16.10 mmol/L being maximum. It was observed that, significantly

higher number of patients had raised CSF lactate levels in pyogenic meningitis ($p<0.001$). The mean CSF lactate levels were significantly high in patients with pyogenic meningitis (12.75 ± 3.46 mmol/L) compared to tubercular (4.11 ± 1.65 mmol/L), cryptococcal (2.93 ± 1.10 mmol/L) and viral (1.98 ± 0.40 mmol/L) ($p<0.001$). Majority of the patients improved (91.43%) while 8.57% of the patients expired.

Conclusion

CSF lactate level was significantly high in pyogenic meningitis and it can provide pertinent, rapid and reliable diagnostic information. Furthermore, CSF lactate level can also differentiate pyogenic andfrom non pyogenic meningitis in a quick and better way.

Keywords

Meningitis; Pyogenic meningitis; Cerebro spinal fluid; CSF Lactate;

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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 which is characterized by inflammation of the meninges which are 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 Pia - 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 meninges that protect the brain and spinal cord. In the brain, meninges 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, about ten times since the access to preventive measures of the disease is still not well developed. Every year, there are about 8000 cases of meningitis in developing countries, and a total number of 2000 deaths occur that mark this disease as high morbidity and mortality. Between the year 1998 and 2003, there was a decline in the cases from 1.5 to 1.9 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 tells us 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]

Meningitis can be classified into three main groups based on the causative agents namely, bacterial/pyogenic meningitis and non pyogenic meningitis due to- viral, tubelcular, fungal etc. Bacterial meningitis is usually caused by Pneumococcal species, Haemophilus influenzae, Staphylococcal species, and meningococcal species. For nonbacterial/non-pyogenic 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 usually found in patients with chronic and debilitating diseases such as, diabetes mellitus, alcoholism, cirrhosis, hypogammaglobulinemia and complement deficiency.[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.[5]

Accurate and rapid diagnosis of acute bacterial meningitis is essential as disease outcome depends on immediate initiation of appropriate antibiotic therapy.[6,7] Bacterial meningitis should be treated promptly with antibiotics, whereas acute aseptic meningitic is usually self limiting. However, differentiating Bacterial meningitis from aseptic meningitis may be challenging for clinicians because the symptoms and laboratory assays are often similar and overlapping. For example, acute meningitis with predominance of neutrophils in CSF suggests BM; however, herpes simplex-1 infected meningitis presents with > 90% neutrophils in CSF.[8] Furthermore, other assays, such as Gram stain, latex agglutination, and polymerase chain reaction-based assays, lack sensitivity.[9-12] In practice, before definitive CSF bacterial cultures are available, most patients with acute meningitis are treated with broad-spectrum antibiotics targeting Bacterial Meningitis. In general, this does not seriously harm the Aseptic Meningitis patient; however, it may enhance the local frequency of antibiotic resistance[13] and cause antibiotic adverse effects, nosocomial infections,[14] and high medical costs.[15] Thus, it is not only important to recognize Bacterial Meningitis patients who promptly need antimicrobial therapy but also Aseptic Meningitis patients who do not need antibiotics and/or hospital stays.[6]

Making a differential diagnosis between bacterial meningitis, aseptic meningitis and tubercular meningitis is a critical clinical problem.[6] Signs and symptoms, results of routine CSF analysis and radiological finding are often inadequate in identifying cause of meningitis.[16] Partially treated bacterial meningitis cultures may be negative and non specific.[16] On CSF analysis the specificity and sensitivity of pleocytosis is low. Culture is the gold standard method (Sensitivity

>80%). However, partially treated patients are negative most of the time and this method is time consuming. PCR method is expensive.[4,17]

In recent years, it has been proposed that CSF lactate may be a good marker that can differentiate bacterial meningitis (> 6 mmol/l), from partially treated meningitis (4 to 6 mmol/l) and aseptic meningitis (< 2 mmol/l).[18] However, other researchers have suggested that CSF lactate offers no additional clinically useful information over conventional CSF markers.[19,20] Other markers, such as C-reactive protein (CRP)[21] and procalcitonin,[22] may allow differentiation of patients with bacterial meningitis from those with aseptic meningitis. Neither of these markers is routinely used in clinical practice.[10]

However, the reported diagnostic accuracy of CSF lactate for the differential diagnosis of Bacterial Meningitis from Aseptic Meningitis has varied across studies.[19,20] The Utility of a CSF lactate assay for this purpose may be considered as it is sensitive (93%) as well as specific (96%) and can be performed rapidly and is cost effective.[23]

This study was planned to estimate CSF lactate as diagnostic marker to differenciate pyogenic meningitis From non-pyogenic Meningitis so as to evaluate its accuracy.

OBJECTIVES

The objective of this study was to estimate CSF lactate as diagnostic marker to differenciate pyogenic meningitis from non-pyogenic Meningitis.

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 *iti* which means "pertaining to". In medical English, the suffix "-itis means" "inflammation of". The membranes surrounding 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.[24]

It is generally caused by infection of viruses, bacteria, fungi, parasites etc. Anatomical defects or weak immune systems may be linked to recurrent bacterial meningitis. In the majority of cases it is caused by a virus. However, some non-infectious causes of meningitis also do exist.[24]

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.[25]

1810 : Reverend Foster gave a graphic description of an outbreak of meningococcemia and meningococcal meningitis.[25]

1863 : Cryptococcosis was recognized.[26]

1882 : The tubercle bacilli were discovered by Robert Koch.[27]

1887 : Weischselbaum described Nisseria meningitidis (N. meningitidis) as the causative agent of meningitis.[28]

1887 : Bruce grew brucella and named it Micrococcus melitensis.[25]

1890 : Bakten showed that meninges could be involved as a result of hematogenous spread.[25]

1891 : Quincke devised the diagnostic lumbar puncture.[25]

1893 : Licktheim isolated tubercle bacilli from CSF.[25]

1893 : Walter showed that the blood CSF barrier to bromide is altered in tuberculous meningitis.[25]

1894 : Cryptococcosis was described in more detail by Busse.[26]

1895 : The fungus was isolated from material of a patient by Busse.[26]

1897 : Bang isolated Brucella abortus.[25]

1913 : Simon Flexner first reported some success in treating bacterial meningitis with intrathecal equine meningococcal antiserum.[29]

1924 : Brucella was first isolated from a patient by Keefer in Baltimore.[25]

1932 : Burr and Finley studied the role of immunity in tuberculous meningitis by injecting tubercle protein in the cisterns of controls and hypersensitive animals.[25]

1933 : Rich and Maccrodale challenged the hematogenous spread after

doing autopsy studies and put forth the Rich focus theory.[25]

1933 : Lancefield introduced her technique for the precipitin grouping of Streptococci.[28]

1958 : Udani and Dastur showed that tuberculous meningitis could present in the form of encephalopathy. [25]

1969 : Dastur and Wadia showed that tuberculous meningitis could present as spinal arachnoiditis.[25]

1980 : Antonine Jesse noticed that tuberculous meningitis was more often associated with tuberculosis (TB) of other organs.[25]

Anatomy of meninges

The brain is covered by three membranous coverings (meninges): The outer is dura mater, the middle is arachnoid mater and inner pia mater. The cerebrospinal fluid fills the space between the arachnoid and 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 divides the cranial cavity into intercommunicating compartments.

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

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

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

Cerebrospinal fluid

Formation and Absorption

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

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

Functions of CSF

- It supports the brain and cerebral venous sinuses.
- It protects the brain from shock.
- It has a nutritive function.

- 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 the commonly used method.

Lumbar puncture

Procedure

The patient lies with his/her back on the edge of the bed in left lateral position with his/her knees drawn up towards his chest. In adults, the L3 to L4 intervertebral space is marked. The part is cleaned with iodine and spirit and anaesthetized with 2% lignocaine and then the spinal needle is inserted aiming towards the patients umbilicus. We will feel resistance while passing through the spinal ligaments and the dura mater. After passing through these structures, we will notice reduced resistance as the needle enters the subarachnoid space. After withdrawing the stylet and holding the needle in position, CSF can be collected. After collecting the required amount of CSF, the needle is withdrawn and the puncture site is sealed with a tincture benzoin seal.[30,31]

Indications

Diagnostic

Absolute

In meningitis and subarachnoid haemorrhage.

Relative

In Multiple sclerosis, Guillain-Barre syndrome(GB syndrome), chronic inflammatory demyelinating polyneuropathy (CIDP), unexplained coma and measurement of CSF pressure.

Therapeutic

- For intrathecal administration of drugs to treat pain and severe spasticity and malignancies.
- For 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 – it is seen that 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 can occur if proper aseptic precautions are not taken.

Pathophysiology

Majority of the cases of meningitis are caused by an infectious agent that has either colonized or established a focus of infection elsewhere in the body of the host. Potential sites of colonization include - skin, nasopharynx, respiratory tract, gastrointestinal (GI) tract, and the genitourinary tract. The organism invades the submucosa at these sites by evading the hosts defenses for eg-physical barriers, local immunity, and phagocytes or macrophages. An infectious agent which is a bacteria, virus, fungus, or a parasite, gains entry to the CNS and causes meningeal disease via any of the 3 following major pathways:

- Invasion of the bloodstream by bacteremia, viremia, fungemia, or parasitemia and subsequent hematogenous seeding of the CNS occurs.

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

- Direct contiguous spread for eg- sinusitis, otitis media, congenital malformations, trauma, or direct inoculation during intracranial manipulation.[32]

Invasion of the bloodstream and subsequent seeding is the most common mode of spread for most agents. This pathway is characteristic of following- meningococcal, cryptococcal, syphilitic, and pneumococcal meningitis. Rarely,

meningitis arises from invasion via- a septic thrombi or osteomyelitic erosion from infected contiguous structures. Meningeal seeding can also occur with a direct bacterial inoculate during trauma, neurosurgery, or instrumentation. Meningitis in the newborn may be transmitted by vertical transmission, involving pathogens that have colonized the maternal intestinal or genital tract, or horizontally, from nursery personnel or caregivers at home.[32]

Local extension from contiguous extracerebral infection (eg, otitis media, mastoiditis, or sinusitis) is the most common cause. Possible pathways for the migration of pathogens from the middle ear to the meninges include -bloodstream, preformed tissue planes (posterior fossa), temporal bone fractures and the oval or round window membranes of the labyrinths.[32]

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 this barrier prevents the immune system from attacking the brain. However, it is seen in meningitis that 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.[32]

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 and worsening of the symptoms of infection.[33]

Depending on the severity of bacterial meningitis, the inflammatory process may remain confined to the subarachnoid space and 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 ongoing inflammatory process. Thus, bacterial meningitis may lead to widespread cortical destruction, particularly when it is left untreated. Replicating bacteria, increasing numbers of inflammatory cells, cytokine-induced disruptions in membrane transport, increased vascular and membrane permeability perpetuate the infectious process in bacterial meningitis. These processes account for the characteristic changes in the 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:[32]

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

Intracranial pressure and cerebral fluid

One of the complication of meningitis is the development of increased intracranial pressure (ICP). The pathophysiology of this complication is complex and it 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 due to release of toxic

factors from the bacteria and neutrophils), and vasogenic edema (increased blood brain barrier permeability) are all thought to play a role in meningitis.[32]

Without medical intervention, the cycle of decreasing CSF, worsening cerebral edema, and increasing ICP will proceed unchecked. Ongoing endothelial injury may result in vasospasm and thrombosis, further compromising CSF, and may lead to stenosis of the large and small vessels. Systemic hypotension due to septic shock also may impair CSF, and the patient soon dies as a consequence of systemic complications or diffuse CNS ischemic injury.[32]

Cerebral edema

The increased CSF viscosity which results from the influx of plasma components into the subarachnoid space and diminished venous outflow leads to interstitial edema. The accumulation of the products of bacterial degradation, neutrophils, and other cellular activation will lead to cytotoxic edema. The ensuing cerebral edema (ie, vasogenic, cytotoxic, and interstitial) significantly contributes to intracranial hypertension and a consequent decrease in the cerebral blood flow. Anaerobic metabolism ensues, which contributes to increase in the lactate concentration and hypoglycorrhachia. In addition, hypoglycorrhachia results from decrease in the glucose transport into the spinal fluid compartment. Eventually, if this uncontrolled process is not modulated by effective treatment then transient neuronal dysfunction or permanent neuronal injury results.[32]

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 in the neuronal damage during occurrences of bacterial meningitis. Increased CSF concentrations of TNF-α, IL-1, IL-6, and IL-8 are characteristic findings seen 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 the 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 ligation of the bacterial components (eg, peptidoglycan and lipopolysaccharide) to pattern-recognition receptors, such as the Toll-like receptors (TLRs).[32]

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-1which was 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 affected with bacterial meningitis. In experimental models of meningitis, they appear early during the course of the 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 the bacterial infection. The chemokine IL-8 mediates neutrophil chemoattractant responses which is induced by TNF-α and IL-1.[32]

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 induction of increased blood-brain barrier permeability. PAF, with its myriad biologic activities, is believed to mediate the formation of thrombi and 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, which leads to the entry of many blood components into the subarachnoid space. In many cases, this contributes to vasogenic edema and elevation of CSF protein levels. In response to the cytokines the neutrophils migrate from the bloodstream and penetrate the damaged blood-brain barrier, producing the profound neutrophilic pleocytosis characteristic of bacterial meningitis.[32]

Genetic predisposition to inflammatory response

The inflammatory response and 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 will cause collateral damage to brain tissue.[32]

Pattern recognition receptors, of which TLR A4 (TLRA4) is the one best studied, lead to increase in the myeloid differentiation 88 (MyD88)-dependent pathway and excessive production of proinflammatory mediators. At present,

dexamethasone is the drug used to decrease the effects of cellular toxicity by neutrophils after they are present. Researchers are now actively seeking ways of inhibiting TLRA4 and other proinflammatory recognition receptors through genetically engineered suppressors.[34]

Bacterial seeding

Bacterial seeding of meninges usually occurs through hematogenous spread. In patients without an identifiable source of the infection, local tissue and bloodstream invasion by bacteria that have colonized the nasopharynx may be the common source. Many of the meningitis-causing bacteria are carried in the nose and throat, often asymptomatically. Most of the meningeal pathogens are transmitted through the respiratory route, including *Neisseria meningitidis* (meningococcus) and *S pneumoniae* (pneumococcus). Once in the bloodstream, the infectious agent must escape the immune surveillance (eg, antibodies, complement-mediated bacterial killing, and neutrophil phagocytosis).[32]

Subsequently, hematogenous seeding into distant sites, including the CNS will occur. The specific pathophysiologic mechanisms by which the infectious agents gain access to the subarachnoid space yet remain unclear. Once inside the CNS, the infectious agents are likely to survive because of the host defenses (eg, immunoglobulins, neutrophils, and complement components) appear to be limited in this body compartment.[32]

Presentation

History

Only about 44% of adults with bacterial meningitis will exhibit the classic triad of fever, headache, and neck stiffness.[35] These symptoms can develop over several hours or over 1-2 days duration. 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.[35]

Other symptoms include nausea, vomiting, photophobia, sleepiness, confusion, irritability, delirium and coma. Approximately 25% of patients with bacterial meningitis present acutely i.e., within 24 hours of the onset of the symptoms. Occasionally, if a patient has been taking antibiotics for another infection, meningitis symptoms can take longer to develop or may be less intense.[32]

Approximately 25% of patients can have concomitant sinusitis or otitis that could predispose to *S pneumoniae* meningitis.[35] In contrast, patients with subacute bacterial meningitis and most patients with viral meningitis present with neurologic symptoms developing over period of 1-7 days. Chronic symptoms lasting longer than 1 week suggests presence of meningitis caused by certain viruses or by tuberculosis, syphilis, fungi (especially cryptococci), or carcinomatosis.[32]

Patients with viral meningitis may have a history of preceding systemic symptoms like myalgias, fatigue or anorexia . Patients with meningitis caused by the mumps virus usually present with the triad of the classic symptoms-fever, vomiting, and headache. This follows the onset of parotitis (salivary gland

enlargement occurs in 50% of patients), which resolves clinically in 7-10 days. As bacterial meningitis progresses, patients of any age can 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 patients.[32]

Atypical presentation may be observed in certain groups. Elderly individuals, especially those with underlying comorbidities like 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 can also have an atypical presentation. Immunosuppressed patients may not show dramatic signs of fever or meningeal inflammation.[32]

A less dramatic presentation of headache, nausea, minimal fever, and malaise may be found in patients with low-grade ventriculitis associated with ventriculoperitoneal shunt. The classic clinical triad of meningitis is fever, headache and nuchal rigidity (stiff neck).

Signs of Meningeal Irritation[32]

Neck rigidity/Neck stiffness

It 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 of the extensor muscles of the neck.

Kernig's Sign

It is tested with the patient supine on the bed by passively extending the patient's knee with the hip in flexed position. In patients with meningeal irritation, this causes pain and spasm of the hamstring muscles.

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 will flex automatically.

TYPES OF MENINGITIS

Various types of meningitis can be categorized according to CSF cytochemical picture as following- neutrophilic meningitis, lymphatic meningitis and aspetic meningitis. Anatomically, meningitis can be divided into inflammation of the duramater (sometimes referred to as pachymeningitis)which is less common, and leptomeningitis which is more common and it is defined as inflammation of the arachnoid tissue and subarachnoid space.

Neutrophilic meningitis

The most common cause of neutrophil predominant meningitis is bacterial infection. Other causes are certain fungal infection like candida, actinomyces and nocardia etc., but these are rare causes of meningitis.

Bacterial meningitis

An acute purulent infection in the sub-arachnoid space. Mostly meninges, sub-arachnoid space and brain parenchyma are all frequently involved in the inflammatory reaction (meaningoencephalitis).

Bacterial meningitis is the most common form of suppurative CNS infection. Currently, the organisms most commonly responsible for community acquired bacterial meningitis are the following- Streptococcus pneumonia, N. Meningitides, group B streptococci and Listeria monocytogenes[8].

In patients with head trauma or neurosurgery, the most common microorganisms are *S pneumoniae* (if CSF leak is present), *Staphylococcus aureus*, enterobacteria, and *Pseudomonas aeruginosa*. In patients with 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 on urgent basis; early shunt removal is usually necessary for cure.[32]

Haemophilus influenzae meningitis

H influenzae is a small, pleomorphic, gram-negative coccobacillus that is commonly 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 infected secretions. Meningitis is the most serious acute manifestation of systemic infection with *H influenza* organism.[32]

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 reported 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 influenza* cases.[36]

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.[36]

Pneumococcal meningitis

S pneumoniae, a gram-positive coccus, is a very common bacterial cause of meningitis. In addition, it is the most common bacterial agent in meningitis associated with skull fracture and CSF leak. It may be associated with other colonized focal infections, such as pneumonia, sinusitis, or endocarditis (as, for example, in Austrian syndrome, which is the triad of pneumococcal meningitis, endocarditis, and pneumonia).[32]

S pneumoniae is a common colonizer of the human nasopharynx and it is present in 5-10% of healthy adults and 20-40% of healthy children. It causes meningitis by escaping the 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 an increased risk for *S pneumoniae* meningitis.[32]

Streptococcus agalactiae meningitis

Streptococcus agalactiae (group B streptococcus [GBS]) is a gram-positive coccus which 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 cases(associated with 70% of cases). Predisposing risks in adults include the following- diabetes mellitus, pregnancy, alcoholism, hepatic failure, renal failure and corticosteroid treatment. In 43% of adult cases, however, no underlying disease is seen.[32]

Meningococcal meningitis

N meningitidis is a gram-negative diplococcus that is carried in the nasopharynx of an otherwise healthy individuals and it initiates invasion by penetrating the airway epithelial surface. The precise mechanism by which this occurs is unclear, but recent viral or mycoplasmal infections have been reported to disrupt the epithelial surface and facilitate invasion by meningococcus.[32]

Most of the 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 in young adults, accounting for about 59% of the cases.[32]

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 rates of mortality, antecedent viral infections, chronic medical illness, use of corticosteroid, active or passive smoking and crowded living conditions, as seen in college dormitories and military facilities, which have been reported in clustering of cases.[32]

Listeria monocytogenes meningitis

Listeria monocytogenes is a small gram-positive bacillus that causes 3% of bacterial meningitis cases and is in association with one of the highest mortalities (20%).[41] Most human cases appear to be food-borne.

L monocytogenes is a common food contaminant, with a recovery rate of about 70% from raw meat and vegetables. Outbreaks are associated with consumption of contaminated coleslaw, milk, cheese, and alfalfa tablets. Groups at risk are- pregnant women, infants and children, elderly individuals (>60 years), adults who are immunosuppressed (eg, steroid users, transplant recipients, or persons with AIDS), Individuals with chronic liver and renal disease and individuals with diabetes.[32]

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.[32]

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.[32]

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.[32]

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.[32]

S epidermidis is the most common cause of meningitis in patients with CNS (ie, ventriculoperitoneal) shunts.[32]

General principles of therapy

There are a number of general principles of antibiotic therapy in patients with bacterial meningitis. The most important initial issues are avoidance of delay in administering therapy and the choice of regimen.

Antibiotic regimen

There are three general requirements antibiotic therapy for bacterial meningitis.

- Use of bacterial drugs effective against the infecting organism.
- Use of drugs that enter the CSF, since the blood-brain barrier prevents macromolecule entry into the CSF.
- Structuring the regimen to optimize bactericidal efficacy based on the
- Pharmacodynamic characteristics of the antimicrobial agent(s).
- Choice of regimen- Antibiotic selection must be empiric immediately after CSF is obtained or when lumbar puncture is delayed. In such patients, antibiotic therapy needs to be directed at the most likely bacteria based upon patient age and underlying comorbid disease. Knowledge of local susceptibility patterns also may be important.

Once the CSF Gram stain results are available, the antibiotic regimen should be tailored to cover the most likely pathogen. If the CSF findings are consistent with the diagnosis of acute bacterial meningitis, but the Gram stain is negative, empiric antibiotic therapy should be continued.

Emperic therapy

The empiric approach to antibiotic selection in patients with suspected bacterial meningitis is directed at the most likely bacteria based on the patients age and host factors[11]. There have been no randomized trials in adult regarding the empiric therapy of bacterial meningitis. Treatment recommendations are based upon in vitro susceptibility and pharmacodynamic data, randomized trials in children, and accumulated clinical experience.

Selected third generation cephalosporins, such as cefotaxime and ceftriaxone are the beta-lactams of choice in the empiric treatment of meningitis. These agents been demonstrated to be superior to cefuroxime and chloramphenicol in randomized trials of bacterial meningitis in children.[37-39] These drugs have consistent CSF penetration and potent activity against the major pathogens of bacterial meningitis, with the notable exceptions of Listeria monocytogenes and some penicillin-resistant strains of S. pneumonia.[40-42] With the worldwide increase in the prevalence of pneumococci, Vancomycin should be added to cefotaxime or ceftriaxone as empiric treatment until culture and susceptibility results are available.[43]

Empiric therapy includes:

- Ceftriaxone – 2 g IV every 12 hours OR
- Cefotaxime – 2 g IV every 4 to 6 hours PLUS
- Vancomycin – 30 to 60 mg/kg IV per day in two or three divided doses PLUS
- In adults >= 50 years of age, Ampicillin – 2 g IV every 4 hours.

Impaired cellular immunity

Among patients with impaired cell-mediated immunity (for example, to lymphoma, cytotoxic chemotherapy, or high-dose glucocorticoids), coverage must be directed against Listeria monocytogenes and gram-negative bacilli (including Pseudomonas aeruginosa) as well as Streptococcus pneumoniae.[44]

An appropriate regimen in patients with normal renal function is

- Vancomycin- 30 to 60 mg/kg IV per day in two or three divided doses PLUS
- Ampicillin – 2 g IV every 4 hours PLUS EITHER
- Cefipime – 2 g IV every 8 hours OR
- Meropenem – 2 g IV every 8 hours.

Nosocomial meningitis

Empiric therapy for nosocomial meningitis must cover both gram-positive and gram-negative (such as Klebsiella pneumonia and Pseudomonas aeruginosa) nosocomial pathogens. An appropriate regimen in patients with normal renal function is:

- Vancomycin – 30 to 60 mg/kg IV per day in 2 or 3 divided doses PLUS
- Ceftazidime – 2 g IV every 8 hours OR
- Cefipime – 2 g IV every 8 hours OR
- Meropenem – 2 g IV every 8 hours

Beta-lactam allergy – The approach to therapy in patients with antibiotic allergies is challenging given the importance of early initiation of therapy and the crucial role of beta-lactam antibiotics in the therapy of bacterial meningitis. Although it is optimal to desentize patients with a history of an IgE-mediated (anaphylactic) reaction to beta-lactams who require therapy with this antibiotic class, an alternative regimen must be used while the desensitization is being performed. Furthermore, the decision

of whether to desensitize a patient should be based on the Gram stain and/or culture data, the latter of which can take several days to yield an organism. For empiric coverage in patients with severe beta-lactam allergies, the following regimen can be used:

- Vancomycin – 30 to 60 mg/kg per day in two or three divided doses PLUS
- Moxifloxacin – 400 mg IV once daily. PLUS
- If Listeria coverage is required (in patients >= 50 and/or in those with defects in cell- mediated immunity or other risk factors), - trimethoprim sulfmethoxazole 10 to 20 mg/kg (of the trimethoprim component) IV per day divided every 6 to 12 hours.

Role of adjunctive Dexamethasone in bacterial meningitis

Initial studies had shown that there was early resolution of symptoms and CSF inflammatory parameters and decreased mortality with use of adjunctive dexamethasone but the difference was not statistically significant. A meta analysis was studied by Van de Beek MD et al which concluded that the benefit of adjunctive dexamethasone for bacterial meningitis patients remains unproven.[45]

Supportive Care

Fluid management – Careful management of fluid and electrolyte balance is important, since both over- and under-hydration are associated with adverse outcomes.

Reduction of intracranial pressure – Patients with bacterial meningitis who have elevations of intracranial pressure, and who are stuporous or comatose, may benefit from insertion of an intracranial pressure monitoring device. Pressure exceeding 20 mm Hg are abnormal and should be treated; there is also rationale for treating smaller pressure elevations (i.e., above 15 mmhg) to avoid larger elevations that can lead to cerebral herniation and irreversible brainstem injury. Methods to reduce intracranial pressure include elevating the head of the bed to 30 degree, hyperventilation to maintain $paCO_2$ between 27 and 30mm Hg, and use of hyperosmolar agents. Reducing intracranial pressure may increase the survival in bacterial meningitis.[46]

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

Lymphocytic meningitis

The most common cause of lymphocyte predominant meningitis is tuberculosis in developing world, other causes are syphilis, lyme disease, cryptococcosis, brucellosis, and other fungal infections etc. Out of all these, tuberculosis remains a major public health problem, mostly seen in age group of 15-59 years. But increasing incidence of human immune deficiency virus HIV, there is a potential for re-emergence of tuberculosis as a significant public health problem in the developed countries as well. It is estimated that 5-10% of all tuberculosis have central nervous system involvement. Of the various maninfestations of CNS tuberculosis, meningitis is the most common (70-80%) followed by tuberculoma. Risk factors for the tuberculosis meningitis include recent acute infectious disease in

children, alcoholism, diabetes, malignancy, chronic corticosteroid administration and AIDS.[47]

The majority of cases of tuberculous meningitis is due to mycobacterium tuberculosis with M.bovis being responsible for less than 5% of cases.[47] Despite the frequency of Mycobacterium avium intracellulare in AIDS cases, few cases of tuberculous meningitis due to nontuberculous mycobacterium have been reported.[48]

Pathogenesis

Tuberculous meningitis arises as a complication of Tuberculosis elsewhere in the body even though extracranial focus is not identifiable in majority of cases. Two stages in the evolution of tuberculous meningitis are described here:

- Initial seeding in the brain or meningitis by haematogenous dissemination of bacilli during primary infection or later from ruptured caseous granuloma.

- Rupture of one of the above subpial caseous tuberculous foci in brain called Rich Focus

The other mechanisms of tuberculous meningitis include

a. Hematogenous dissemination during primary infection / miliary tuberculosis

b. Direct extension from adjacent extracranial sites like mastoiditis tuberculosis of spine or skull bones.

c. Intracranial lymphatic spread from cervical lymphoids.

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

Pathology

Pathologically tuberculous meningitis is a meningoencephalitis rather than pure meningitis. The three pathologic features of tuberculous meningitis are

a. Inflammatory meningeal exudates.

b. Vasculitis of arteries traversing the exudates.

c. Disturbance of cerebrospinal fluid flow causing hydrocephalus.

d. Hydrocephalus is almost always present when the patient survives more than 4 to 6 weeks. It may be asymmetrical or symmetrical.

e. Hydrocephalus develops early and is much more frequent and severe in children than it is in adults.

f. Immune complexes were found in a fair number of tuberculous meningitis cases indicating that antigen antibody reaction and hypersensitivity plays very important role in causation of various symptoms.

Clinical Features

In the pre-chemotherapeutic era, tuberculous meningitis followed a relentlessly progressive clinical course.

Medical Research Council (MRC) staging of TBM.[48,49]

- Stage 1: Prodromal phase with no definite neurological symptoms or signs.
- Stage 2: Signs of meningitis irritation with slight or no clouding of consciousness and minor (cranial) nerve palsies or neurological deficits.
- Stage 3: Severe clouding of consciousness, stupor, coma, convulsions, and gross paresis or involuntary movements

Diagnosis

Clinical suspicion supported by careful CSF analysis is the only method even today for the diagnosis of tuberculous meningitis. CSF analysis plays a pivotal role in the diagnosis of tuberculous meningitis. Opening pressures are often but not invariably elevated.[50]

Classically the CSF in tuberculous meningitis is clear, colorless and may show a pelilicle or cobweb clot. On standing high protein levels can make CSF appear xanthochromic. The protein levels in CSF usually range from 100-500 mg%. Initial level of more than 300mg% correlates with poor prognosis. In advanced cases due to spinal block, xanthochromia can develop with protein content of 1000-1500 mg%.

CSF glucose is below 40mg per dl or 50% of the parallel blood sugar value, though it is never as low or absent as in pyogenic meningitis. CSF chloride value does not have any diagnostic or prognostic value.

Microscopic examination of CSF reveals pleocytosis usually not exceeding 500 cells per mm^3. Majority of cells are lymphocytes. In the early stages polymorphonuclear reaction can be observed which is replaced by lymphocytes in a

period of weeks if untreated. Like the clinical picture CSF responses may be atypical. CSF changes are dependent on the degree of sensitivity of the patient and the amount of tuberculin in CSF. The CSF picture initially may be normal or mimic pyogenic meningitis.

Hemorrhagic CSF suggesting subarachnoid hemorrhage has also been recorded. In patients with AIDS and tuberculous meningitis CSF protein may be normal and occasionally acellular.

Contemplated confirmatory diagnosis tests:

These include tests based on detection of the mycobacterium

i. CSF smear for AFB

ii. CSF culture for AFB

Demonstration of AFB in CSF is the single most important procedure for a definitive diagnosis. CSF smear for AFB is positive in 5-37% cases and the CSF culture for AFB is positive in 40-80% cases.[51,52]

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

It is tedious and time consuming to grow tubercle bacilli on culture. Routine methods require 3 to 8 weeks. The radiometric methods are much quicker and give results within a few days. A variety of PCR methods have been developed for detection of specific sequence of M. tuberculosis and other mycobacteria. A PCR

assay system for tuberculosis, which is commercially available has been found to be reproducible, sensitive as well specific. As compared to 5-20 percent positively with demonstration of AFB and mycobacterial cultures, PCR has been found to be positive 50-70 percent of specimens from cases having cardinal features as well biochemical/ cytological evidence of neurotuberculosis.[53-55]

Management

The development of specific chemotherapeutic agents revolutionized the prognosis of tuberculosis making it curable and preventable. However for a variety of reasons related to prolonged drug intake and consequent problems of compliance and drug resistance, the promise of chemotherapy for tuberculosis is not fully realized.

Treatment regimen

The world health organization put CNS tuberculosis under treatment category 1 and recommended initial phase therapy (2 months) with isoniazid rifampicin, ethambutol and pyrazinamide followed by continuation phase (4 months) with isoniazid and rifampicin.

When organism are resistant to more than one drug treatment should be tailored according to the susceptibility data. The general guidelines is to introduce atleast two new drugs to which organisms is susceptible. The treatment is empirically continued for two years.

Duration of therapy

Since neuro tuberculosis is usually a sequel to occult or obvious pulmonary infection, the results of studies from pulmonary tuberculosis have been extrapolated to CNS tuberculosis, the main contending factor being CSF penetrance. Poor CSF penetrance of most drugs makes it necessary to continue the treatment for longer periods than required in pulmonary tuberculosis.

The current recommendation is that tuberculosis meningitis be treated for one year or 9 months[41]. Though preliminary reports of the adequacy of a six month treatment are now available, the incidence of the neurological sequelae in these reports in these reports makes it wise to continue therapy for 12 months.

Corticosteroids have been found to be most beneficial in patients with complications of TBM including raised intracranial pressure, hydrocephalalus, stupor, focal neurological signs due to arteritis spinal block and basal optochiasmatic pachymeningitis.

Syphilitic meningitis

The major clinical categories of symptomatic neurosyphilis include meningeal, meningovascular, and parenchymatous syphilis. For meningeal syphilis the onset of symptoms usually occurs within one year of infection. It may involve either the brain or the spinal cord, and patients may present with headache, nausea, vomiting neck stiffness, cranial nerve involvement, seizures, and changes in mental status.

Patient presenting with uveitis or iritis frequently have meningeal syphilis. The CSF shows pleocytosis (>5 white blood cells/cmm), increased protein concentration, and VRDL reactivity. The CSF VRDL is highly specific but is insensitive. CSF-FTA test may be used to rule out neurosyphilis.

Neurosyphilis is treated with intravenous penicillin for 10-14 days.

Cryptococcal meningitis

Cryptococcus neoformans, yeast like fungus, is the etiological agent of cryptococcosis. Infection is acquired by inhalation of aerosolized infectious particles. Cryptococcosis usually presents clinically as chromic meningoencephalitis. CNS involvement usually presents as signs and symptoms of chronic meningitis such as headache, fever, lethargy, and cranial nerve palsies etc.[56]

The classical CSF abnormalities are lymphocytic pleocytosis, elevated protein, and visualization of fungal capsule with India ink preparation or detection of cryptococcal antigen test. The condition is treated with intravenous amphotericin-B with or without fluconazole.[57]

Aseptic meningitis

The most common cause of aseptic meningitis is viral infection, other causes are carcinomatous meningitis and drug induced hypersensitivity reactions. The most important viruses are enteroviruses (coxsackieviruses, echoviruses, human enteroviruses 68-71), herpes simplex virus-2, arthropod borne viruses, and HIV etc.[58]

Patients with viral meningitis usually present with headache, fever, and signs of meningeal irritation coupled with inflammatory CSF profile. The typical profile is a lymphocytic pleocytosis with a low glucose concentration, normal or mildly elevated protein level.[59] As a rule, a lymphocytic pleocytosis with a low glucose concentration should suggest fungal, tuberculosis or non-infectious (sarcoid, neoplastic) meningitis. Though oral or intravenous acyclovir may be of benefit in patients with meningitis caused by HSV-1 or -2 and in cases of severe EBV or VZV infection, mainstay of therapy is supportive.

CSF lactate and its role in meningitis

CSF lactate is produced by anaerobic metabolism and the level increases in any condition which causes decrease in oxygen supply to the brain and there is no correlation with serum lactate level.[60]

CSF lactate in bacterial meningitis originates from different sources. Bacterial pathogens themselves produce varying amounts of lactate and accounts for 10% of the total CSF lactate.[61] Bacterial meningitis is associated with generalized brain oedema, causing a reduction of global cerebral blood flow and inflammatory involvement of vasculature, with loss of autoregulaory mechanisms, vasospasm and thrombosis. This leads to cerebral ischaemia and consequently to glycolysis by means of anaerobic metabolism. In addition, cytokines that flood the brain in meningitis, reduce tissue oxygen uptake and cause a shift toward anaerobic metabolism, thus increasing lactate production.

Cytokines also mediate invasion of neutrophils into the subarachnoid space, which may also contribute to the rise in CSF lactate level by glycolysis in bacterial meningitis.[62]

The CSF lactate level of 3.5 mmol/l or greater has been considered by the some authors superior to the other CSF tests to diagnose and differentiate pyogenic and non-pyogenic meningitis.

However, other studies show that the elevated CSF lactate level is a non specific finding and occurs in number of diseases such as meningitis, hypoxic cerebral injury, subarachnoid haemorrhage and head injury.[63]

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, Belagavi.

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 2015 to December 2015.

Place

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

Source of Data

Patients presenting with meningitis to the Department of Medicine and Neurology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi were studied.

Sample size

A total of 70 patients presenting with meningitis were selected for the study.

Sampling procedure

The sample size was calculated using the following formula.

$n = 4\ za^2\ p\ q\ /\ d^2$

Where, 4Za = constant (1.96)

p = sensitivity obtained from previous studies that is, 55% by Ali Hassan Abro et al.[64] on CSF lactate level as a diagnostic tool to differentiate acute bacterial from viral meningitis, at Infectious disease dept., Rashid Hospital Dubai.

q = 100 – p = 45%

d = Absolute error considered as 15%

Considering the above values the sample size obtained was 70. Hence a minimum sample size of 70 cases was planned.

Selection criteria

Inclusion

- All clinically suspected cases of meningitis admitted to KLE hospital that is, any one of the following
- **CSF Pleocytosis:**[4]
    - Pyogenic (>1000cells/microL)
    - Tubercular (25-100cells/microL)
    - Viral (25-500cells/microL)
    - Fungal(40-600cells/microL)
- **CSF Protiens**[4]
    - Pyogenic (>100mg/dl)

- Tubercular (100-200mg/dl)
- Viral(20-80mg/dl)
- Fungal (>150-300mg/dl)

- **CSF Sugars**[4]
  - Pyogenic (<40mg/dl)
  - Tubercular:(<50mg/dl in 75% cases)
  - Viral:normal(40-85mg/dl)
  - Fungal: decreased to normal(40-85mg/dl)
- **Cell type**:[4]
  - Lymphocytic/Neutrophilic Pleocytosis.
- **CSF** LACTATE: Normal: 0.6-2.2mmol/L[65]
- **CSF**
  - INDIA INK, ADA, GRAM staining, ZN staining , culture and others as required.

Exclusion

- Patient with conditions which can contribute in elevation of CSF lactate such as stoke, brain hypoxia, head injury and subarachnoid hemorrhage.

Ethical clearance

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

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

Demographic data such as age, sex clinical presentation and history pertaining to the other comorbid conditions and drugs history 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. The diagnosis of meningitis was made on the basis of clinical symptoms and signs like headache, fever, nausea, vomiting, neck rigidity, presence of kernig's sign and or brudzinski's sign, altered sensorium any focal neurological defect, cranial nerves palsies, hemiparesis, seizures and/or signs of cerebral dysfunction ranging from confusion, delirium, declining level of sensorium from lethargy to coma. Lumbar puncture was performed on the patients on day of admission. CSF lactate analysis was done for all cases with abnormal CSF cytochemical picture. These findings were recorded on a predesigned and pretested proforma (Annexure II).

Investigations

The patients were evaluated for following investigations

- CSF cytochemical analysis including cell counts, cell type, protein, sugar.
- CSF Gram stain and Z.N stain.

- CSF LACTATE LEVEL.
- Blood culture and CSF culture.
- Screening for HIV.
- Complete blood count.
- CSF (INDIA INK, ADA and others) if indicated.
- LFT, RFT, Ser. Electrolytes,RBS if indicated
- CT/MRI if indicated.

Estimation of CSF lactate

CSF lactate analysis was done for all the cases with abnormal CSF cytochemical picture.

Estimation of CSF analysis was done using Dimension Clinical chemistry system Flex reagent cartridge (Issue date 2008-02-20) Based on manufacturers recommendation the expected normal range was considered between 0.6-2.2 mmol/L.[65]

Cases were divided into pyogenic and nonpyogenic meningitis groups based on following criteria.

Pyogenic meningitis

CSF showing neutrophillic pleocytosis (>1000cells/microL), raised protein (>100mg/dl), low sugars (<40 mg/dl) with or without bacteria demonstrated on Gram stain/culture.

Non pyogenic meningitis

Tubercular meningitis

CSF showing lymphocytic pleocytosis (25-100cells/microL), raised protein (100-200mg/dl), low sugars(<50mg/dl in 75% cases) with high CSF ADA levels with or without bacteria demonstrated on ZN staining/culture.

Viral meningitis

CSF showing lymphocytic pleocytosis (25-500cells/microL), normal/slightly raised protein(20-80mg/dl), normal sugars with absent/normal CSF ADA levels and negative for bacteria on microscopy/cultures.

Fungal meningitis

CSF showing lymphoytic pleocytosis, raised protein (150-300mg/dl), sugars decreased to normal(40-85mg/dl), India ink present

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 independent 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.

RESULTS

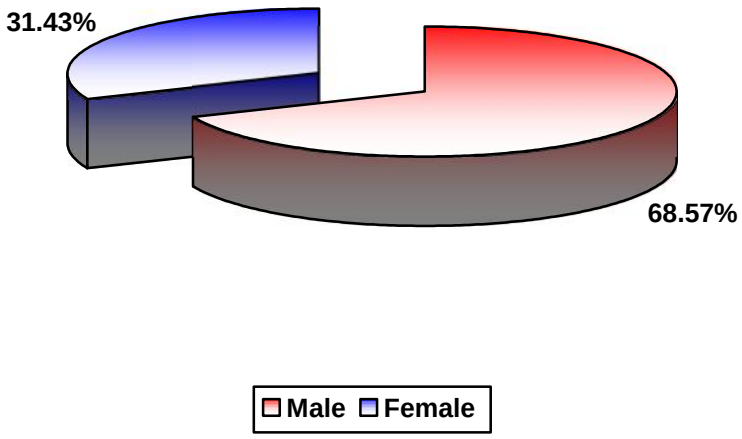
The present one year cross-sectional study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2015 to December 2015.A total of 70 clinically suspected cases of meningitis patients presenting to department of medicine and neurology at KLES Dr Prabhakar Kore Hospital Belgaum were subjected to Lumbar puncture, and was performed on the day of admission.

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

Table 1. Distribution of cases according to the sex

Sex	Distribution (n=70)	
	Number	**Percentage**
Male	48	68.57
Female	22	31.43
Total	**70**	**100.00**

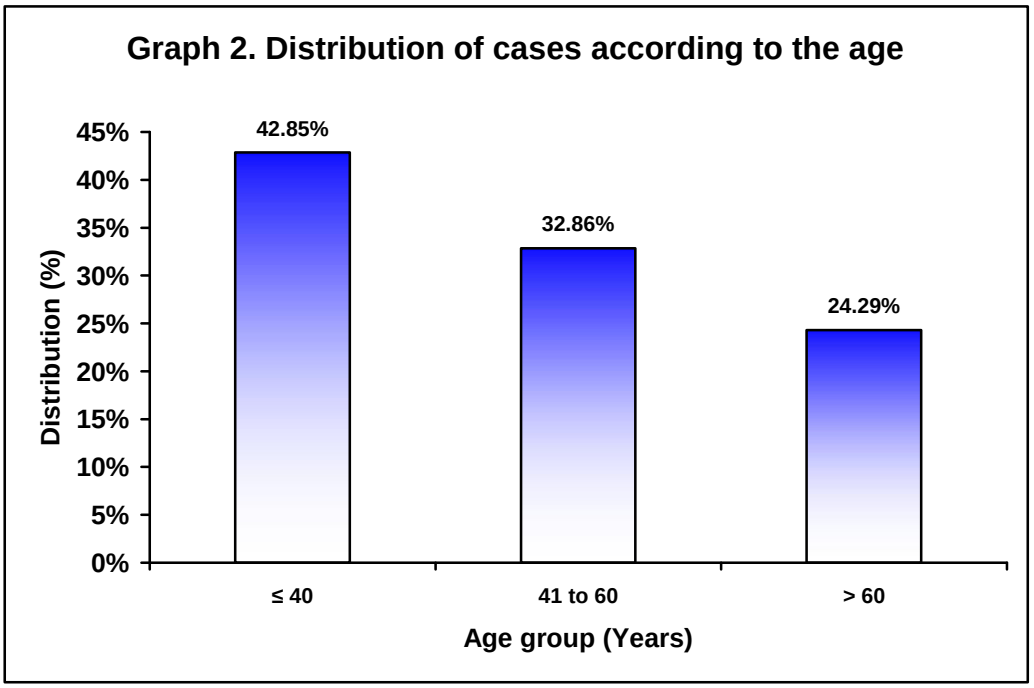
Graph 1. Distribution of cases according to the sex



In the present study 68.57% of the patients were males and 31.43% were females. Male to female ratio was 2:1.

Table 2. Distribution of cases according to the age

Age group (Years)	Distribution (n=70)	
	Number	**Percentage**
≤ 40	30	42.85
41 to 60	23	32.86
> 60	17	24.29
Total	**70**	**100.00**

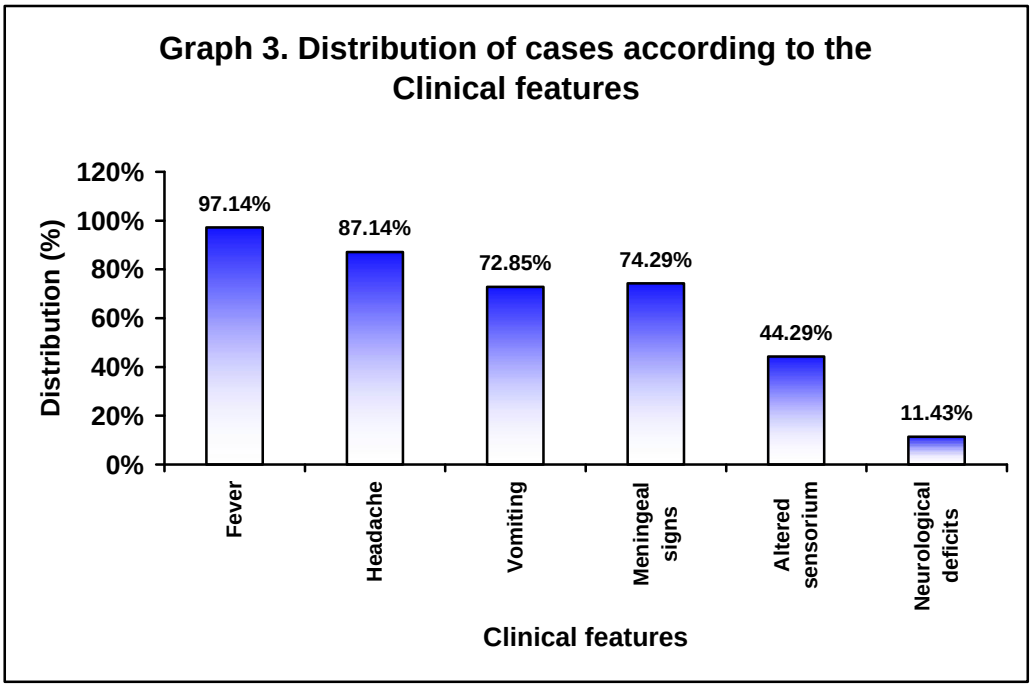


In this study age ranged from 18 to 88 years. The mean age was 46.51 ± 18.90 years. Most of the patients were aged between ≤ 40 years (42.85%) followed by 41 to 60 years (32.86%) and > 60 years (24.29%).

Table 3. Distribution of cases according to the clinical features

Clinical features	Distribution (n=70)	
	Number	Percentage
Fever	68	97.14
Headache	61	87.14
Vomiting	51	72.85
Altered sensorium	31	44.29
Meningeal signs	52	74.29
Neurological deficits	8	11.43

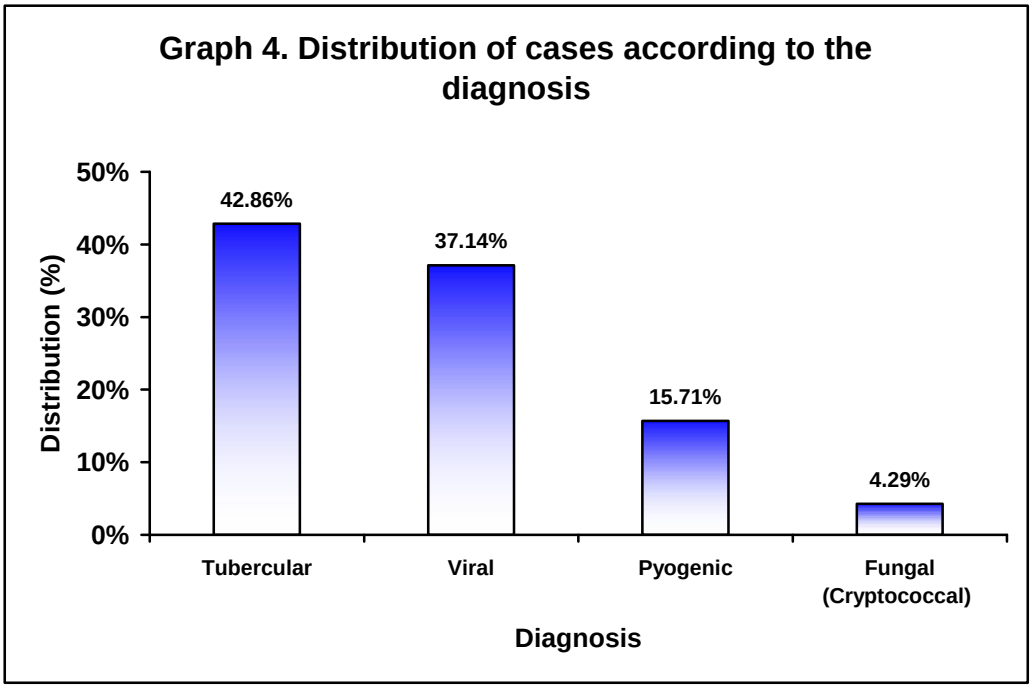
Multiple features hence total not shown



In the present study most common clinical presentation was fever noted in 97.14% of the patients. The other common presentations were headache (87.14%) and Vomiting (72.85%). Presence of meningeal signs was noted in 74.29% of the patients while altered sensorium was noted in 44.29% of the patients and neurological deficits were noted in 11.43% of the patients.

Table 4. Distribution of cases according to the diagnosis

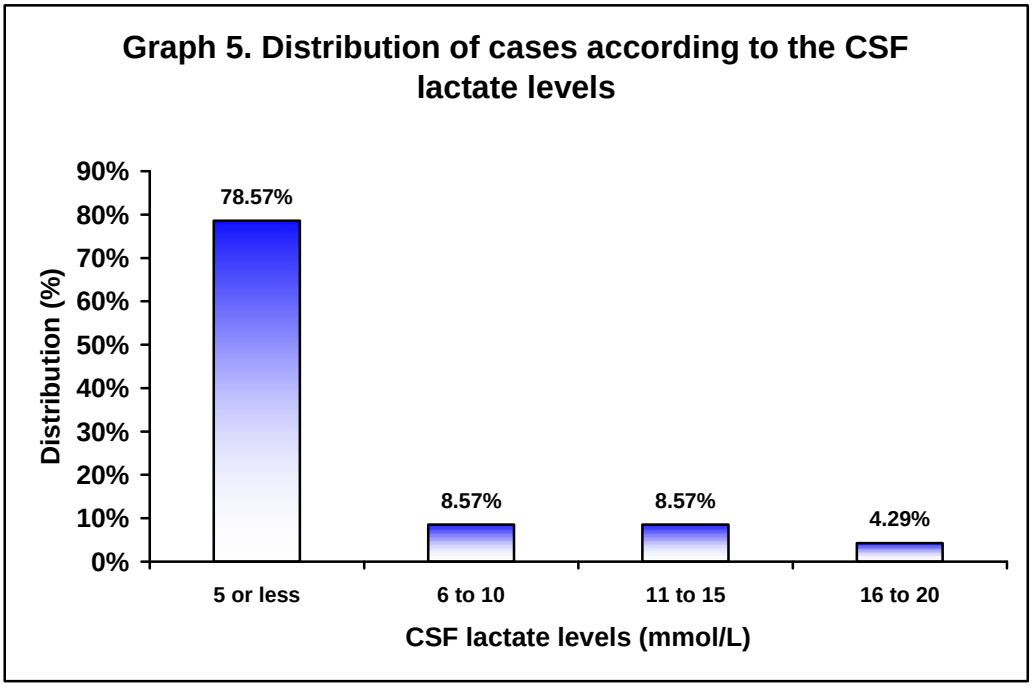
Diagnosis	Distribution (n=70)	
	Number	**Percentage**
Tubercular	30	42.86
Viral	26	37.14
Pyogenic	11	15.71
Fungal (Cryptococcal)	3	4.29
Total	**70**	**100.00**



In the present study most of the patients had tubercular meningitis (42.86%) followed by viral (37.14%), pyogenic (15.71%) and Fungal (Cryptococcal) (4.29%).

Table 5. Distribution of cases according to the CSF lactate levels

CSF lactate levels (mmol/L)	Distribution (n=70)	
	Number	**Percentage**
5 or less	55	78.57
6 to 10	6	8.57
11 to 15	6	8.57
16 to 20	3	4.29
Total	**70**	**100.00**



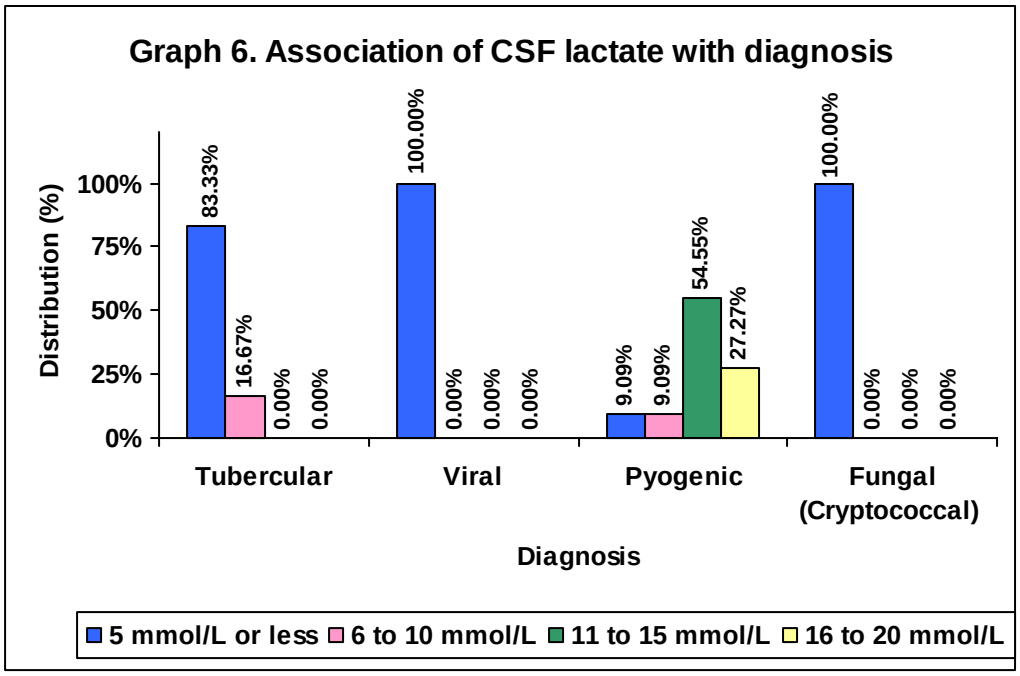
[Normal level of CSF lactate:0.6-2.2mmol/L]

In this study majority of the patients had CSF lactate levels of ≤5 mmol/L (78.57%) while lactate levels of 6 to 10 mmol/L, 11 to 15 mmol/L and 16 to 20 mmol/L were noted in 8.57%, 8.57% and 4.29% of the patients respectively. The mean CSF lactate levels were 4.66 ± 4.07 mmol/L and median levels were 2.70 mmol/L with range 1 mmol/L being minimum and 16.10 mmol/L being maximum.

Table 6. Association of CSF lactate with diagnosis

Diagnosis	CSF lactate levels (mmol/L)								Total	
	5 or less		6 to 10		11 to 15		16 to 20			
	No	%	No	%	No	%	No	%	No	%
Tubercular	25	83.33	5	16.67	0	0.00	0	0.00	30	100.00
Viral	26	100.00	0	0.00	0	0.00	0	0.00	26	100.00
Pyogenic	1	9.09	1	9.09	6	54.55	3	27.27	11	100.00
Fungal (Cryptococcal)	3	100.00	0	0.00	0	0.00	0	0.00	3	100.00
Total	**55**	**78.57**	**6**	**8.57**	**6**	**8.57**	**3**	**4.29**	**70**	**100.00**

p = <0.001

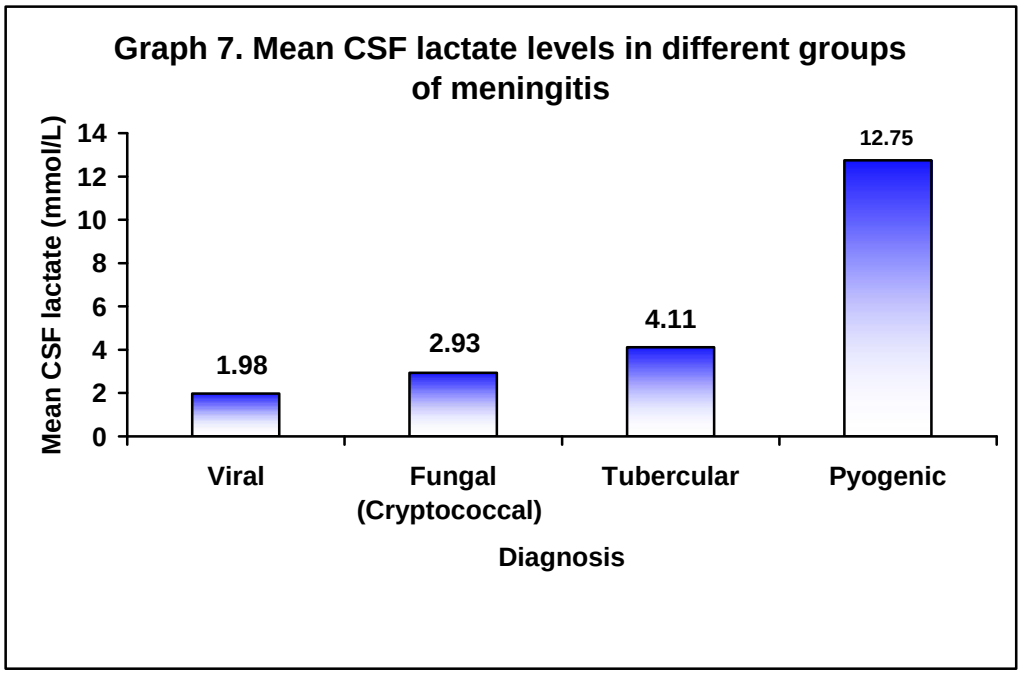


The Association of lactate levels in different type of meningitis is as depicted in table 6. It was observed that, significantly higher number of patients had raised CSF lactate levels in pyogenic meningitis (p<0.001)

Table 7. Mean CSF lactate levels in different groups of meningitis

Diagnosis	Diagnosis	CSF lactate (mmol/L)	
		Mean	SD
Viral	26	1.98	0.40
Fungal (Cryptococcal)	3	2.93	1.10
Tubercular	30	4.11	1.65
Pyogenic	11	12.75	3.46
F value		99.293	
P value		<0.001	

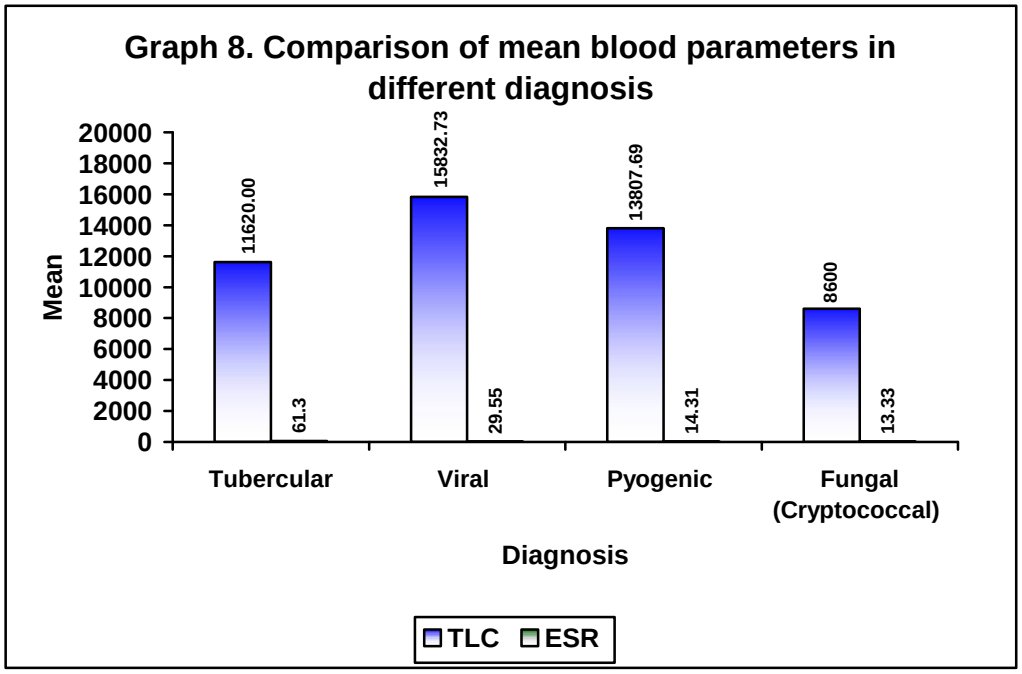
p<0.001



In the present study mean CSF lactate levels were significantly high in patients with pyogenic meningitis (12.75 ± 3.46 mmol/L) compared to tubercular (4.11 ± 1.65 mmol/L), cryptococcal (2.93 ± 1.10 mmol/L) and viral (1.98 ± 0.40 mmol/L) (p<0.001).

Table 8. Comparison of mean blood parameters in different diagnosis

Blood parameters	Type of meningitis	(n)	Mean	SD	Min	Max	F Value	p value
TLC	Tubercular	30	11620.00	4229.40	5200	20400	**0.673**	**0.572**
(Cells/m^3)	Viral	26	15832.73	2943.91	4600	90900		
	Pyogenic	11	13807.69	16207.38	10400	20060		
	Fungal (Cryptococcal)	3	8600.00	4156.92	3800	1100		
ESR	Tubercular	30	61.30	21.95	14	105	**33.113**	**<0.001**
	Viral	26	29.55	24.26	6	51		
	Pyogenic	11	14.31	9.62	6	105		
	Fungal (Cryptococcal)	3	13.33	2.89	10	15		



The comparison of blood parameters in different type of meningitis is as shown in Table 8. It was noted that TC was comparable in different types of meningitis but ESR was significantly high in patients with tubercular meningitis ($p<0.001$).

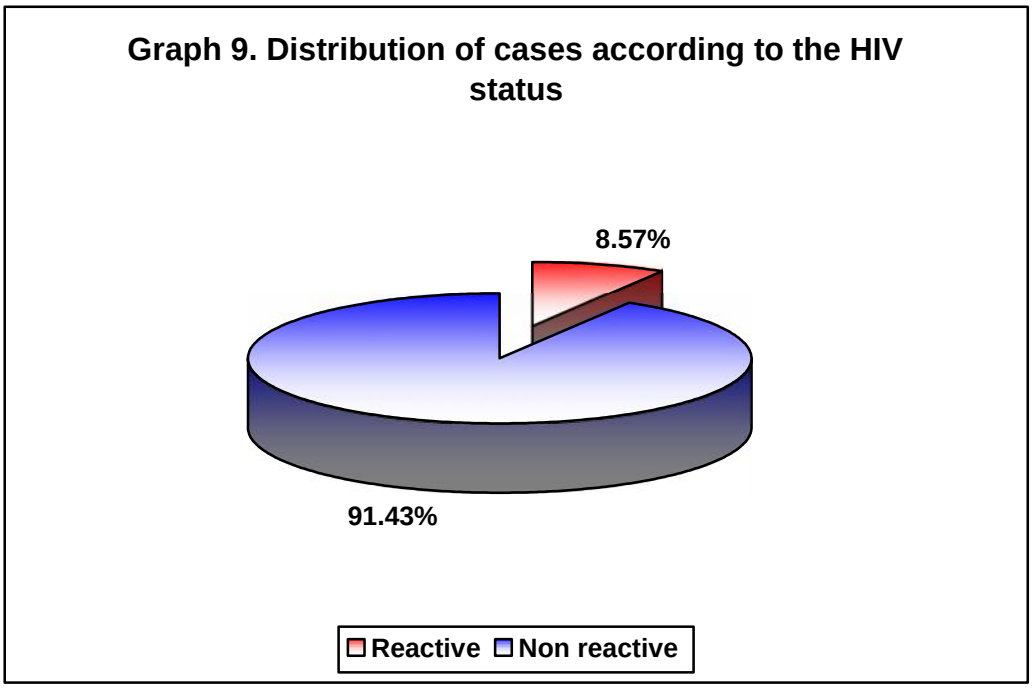
Table 9. Comparison of mean CSF parameters in different types of meningitis

Blood parameters	Type of meningitis	(n)	Mean	SD	Min	Max	F Value	p value
TC	Tubercular	30	443.10	197.43	20	750	99.427	**<0.001**
	Viral	26	41.88	101.34	5	530		
	Pyogenic	11	1220.00	322.54	5	530		
	Fungal (Cryptococcal)	3	126.00	66.84	70	200		
PMN	Tubercular	30	23.83	26.90	0	100	38.941	**<0.001**
	Viral	26	12.12	15.57	0	40		
	Pyogenic	11	90.00	3.87	5	20		
	Fungal (Cryptococcal)	3	16.67	20.21	5	40		
Lymphocyte	Tubercular	30	76.17	26.90	0	100	38.941	**<0.001**
	Viral	26	87.88	15.57	60	100		
	Pyogenic	11	10.00	3.87	5	20		
	Fungal (Cryptococcal)	3	83.33	20.21	60	95		
Glucose	Tubercular	30	56.64	19.64	25	110.20	11.712	**<0.001**
	Viral	26	65.73	13.54	44	97		
	Pyogenic	11	29.55	16.53	10	62		
	Fungal (Cryptococcal)	3	59.00	18.19	48	80		
Protein	Tubercular	30	132.42	109.39	41.5	618	10.219	**<0.001**
	Viral	26	53.39	19.72	28	135.5		
	Pyogenic	11	267.82	215.67	93	856.4		
	Fungal (Cryptococcal)	3	213.93	27.85	195.8	246		
Lactate	Viral	26	1.98	0.40	2.2	7.8	99.293	**<0.001**
	Fungal (Cryptococcal)	3	2.93	1.10	2.2	4.2		
	Tubercular	30	4.11	1.65	1.0	2.7		
	Pyogenic	11	12.75	3.46	4.8	16.1		

Table 9 shows comparison of means CSF blood parameters. It was observed that, All the CSF variables including TC, PMN, Lymphocyte, glucose, proteins varied significantly in different diagnosis ($p<0.001$).

Table 10. Distribution of cases according to the HIV status

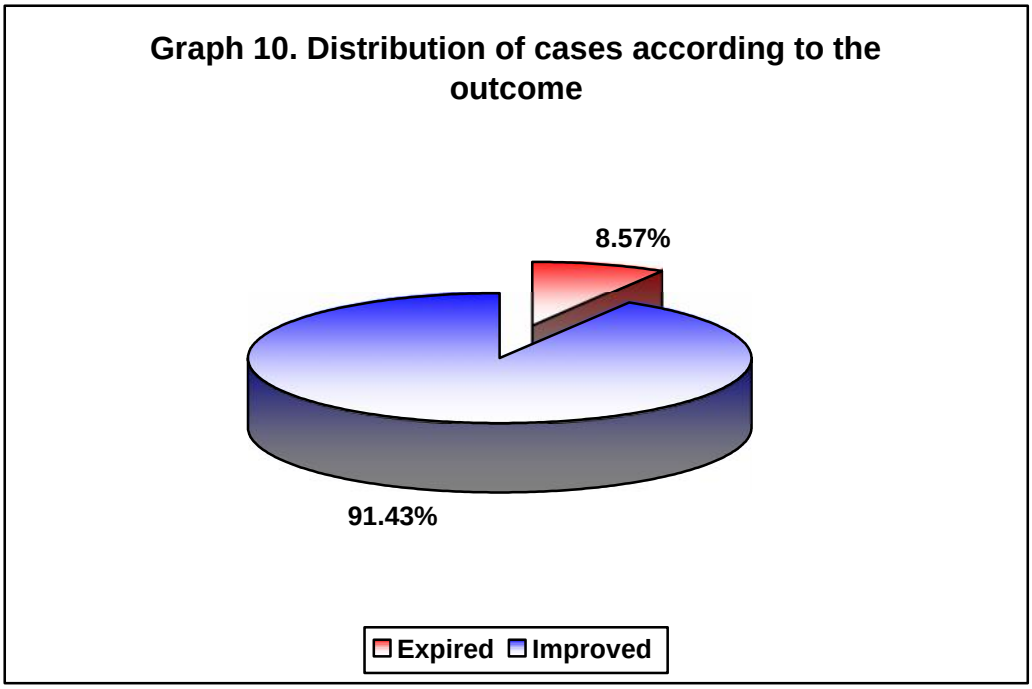
HIV Status	Distribution (n=70)	
	Number	**Percentage**
Reactive	6	8.57
Non reactive	64	91.43
Total	**70**	**100.00**



In the present study HIV test was reactive in 8.57% while in 91.43% of the patients it was non reactive.

Table 11. Distribution of cases according to the outcome.

Outcome	Distribution (n=70)	
	Number	**Percentage**
Expired	6	8.57
Improved	64	91.43
Total	**70**	**100.00**

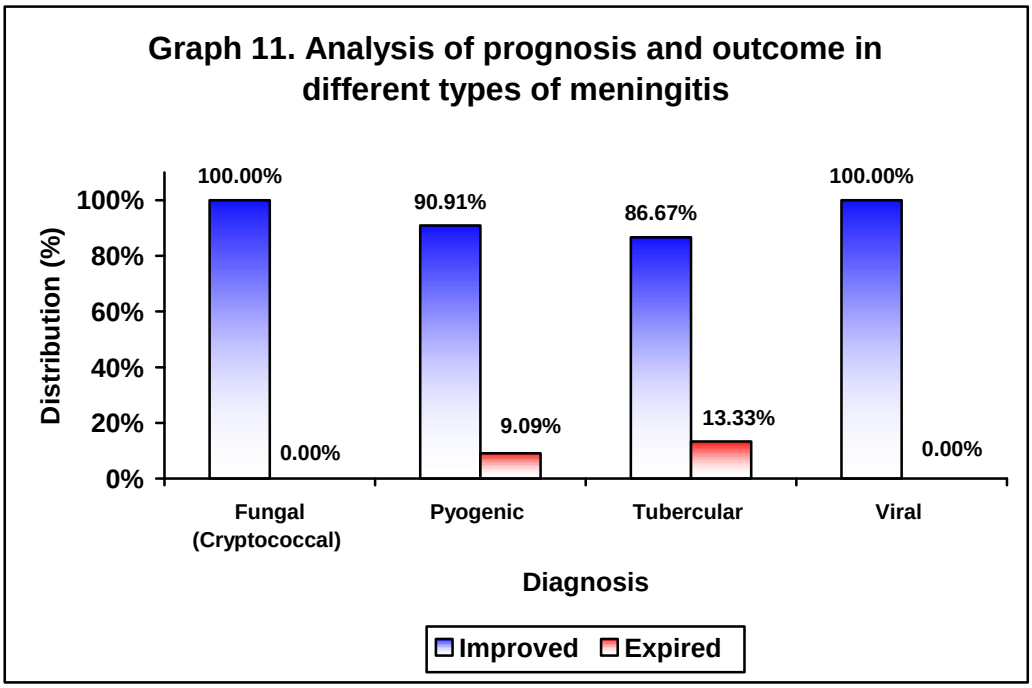


In the present study majority of the patients improved (91.43%) while 8.57% of the patients expired.

Table 12. Analysis of prognosis and outcome in different types of meningitis

Diagnosis	Outcome				Total	
	Improved		Expired			
	No	%	No	%	No	%
Fungal (Cryptococcal)	3	100.00	0	0.00	3	100.00
Pyogenic	10	90.91	1	9.09	11	100.00
Tubercular	26	86.67	4	13.33	30	100.00
Viral	26	100.00	0	0.00	26	100.00
Total	**65**	**92.86**	**5**	**7.14**	**70**	**100.00**

p=0.192



In this study mortality was high in patients with tubercular meningitis (13.33%) compared to pyogenic meningitis (9.09%). However this difference was statistically not significant (p=0.192).

DISCUSSION

Meningitis is an inflammation of the protective membranes covering the brain and spinal cord which are collectively known as the meninges.[66] It can lead to serious long-term consequences such as, deafness, epilepsy, hydrocephalus and cognitive deficits especially if not treated quickly.[67]

The most important test in identifying or ruling out meningitis is analysis of the cerebrospinal fluid.[68] 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.[69]

The desirability of avoiding unnecessary administration of antibiotics to non-infected patients, the potentially devastating consequences associated with administration of corticosteroids to patients with aseptic meningitis,[70] and the need to establish diagnostic usefulness of CSF lactate has prompted this study.

This one year cross-sectional study was carried out in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi. A total of 70 patients presenting with meningitis aged more than 18 years were studied.

In the present study 68.57% of the patients were males and 31.43% were females. Male to female ratio was 2:1 suggesting male preponderance. These findings were similar to a study done by Holub M. et al.[71] where the meningitis was

noted in 61.7% of males and in females was 38.3%. A similar study by Abro AH et al.[64] from UAE in 2009 also reported male predominance, with 84.21% of males and 15.78% of the females.

In this study nearly half of the study population belonged to the age group between 18 to 40 years (42.85%) followed by 41 to 60 years (32.86%) and > 60 years (24.29%). The mean age was 46.51 ± 18.90 years while median age 45.50 years with range 18 years being minimum and 88 years being maximum. The mean age observed in the present study was slightly high compared to the study by Abro AH et al.[64] who reported the mean age of the patients as 34 ± 11.5 years and age ranged between 15-70 years. Holub M et al.[71] observed the mean age of 42 years in his study which was comparable with the present study.

In the present study most common clinical presentations were fever (97.14%) followed by headache (87.14%) and Vomiting (72.85%). Presence of meningeal signs was noted in 74.29% of the patients while altered sensorium was noted in 44.29% of the patients while neurological deficits were noted in 11.43% of the patients. Abro AH et al.[64] in their study reported Fever, headache and altered sensorium were as the most common presenting symptoms. A study by Van de Beek D et al[72] reported the classic triad of fever, 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%.

In this study the most common type of meningitis noted was tubercular meningitis comprised of 42.86% of the patients. The next common diagnosis was

viral meningitis noted in 37.14% of the patients, followed by pyogenic meningitis (15.71%) and cryptococcal meningitis (4.29%).

The information yielded by examination of Cerebrospinal fluid (CSF) is often of crucial importance in the diagnosis of neurological disease.[73] In the present study, CSF lactate levels ranged between 1 mmol/L to 16.10 mmol/L. The mean CSF lactate levels were 4.66 ± 4.07 mmol/L and median levels were 2.70 mmol/L. Majority of the patients that is, 78.57% had CSF lactate levels of ≤5 mmol/L while 8.57% of the patients each had lactate levels of 6 to 10 mmol/L, and 8.57% the patients the lactate levels ranged between 11 to 15 mmol/L, and in 4.29% of the patients lactate levels were 16 to 20 mmol/L.

The presents study showed significant association between high CSF lactate levels with pyogenic meningitis as significantly higher number of patients with pyogenic meningitis had raised CSF lactate levels that is 54.55% of the patients with pyogenic meningitis had CSF lactate levels between 11 to 15 mmol/L and 27.27% of the patients had CSF lactate levels between 16 to 20 mmol/L while only 9.09% each of the patients had CSF lactate levels ≤5 and 6 to 10 mmol/L while in patients with tubercular, viral and cryptococcal meningitis none of the patient had CSF lactate levels between 11 to 15 mmol/L and 16 to 20 mmol/L. This difference was statistically significant ($p<0.001$). This positive association prompted the comparison of mean CSF levels. It was observed that, mean CSF lactate levels were significantly high in patients with pyogenic meningitis (12.75 ± 3.46 mmol/L) compared to tubercular (4.11 ± 1.65 mmol/L), cryptococcal (2.93 ± 1.10 mmol/L) and viral (1.98 ± 0.40 mmol/L) ($p<0.001$). It was evident that patients with pyogenic meningitis has profoundly raised CSF lactate levels to the extent of 2 to 3 fold

compared to tubercular, cryptococcal and viral meningitis. These findings suggest that, patients with pyogenic meningitis are likely to present with significantly raised CSF lactate levels and can provide pertinent, rapid and reliable diagnostic information to the treating physician. These findings were in agreement with a study by Abro AH in UAE and several other studies

A study by Abro AH et al.[64] in UAE to evaluate the potential role of CSF lactate level in the diagnosis of acute bacterial meningitis and in the differentiation between viral and bacterial meningitis where, the CSF analysis showed, all patients with bacterial meningitis had lactate level more than 3.8 mmol/L except one patient who had CSF lactate 1.6 mmol/L, whereas of patients with viral meningitis, none had CSF lactate > 3.8 mmol/L. In comparison to viral meningitis, bacterial cases had significantly high CSF lactate level, with mean lactate level of 16.51 ± 6.1 mmol/L (range 1.6-35.5) versus 2.36 ± 0.6 mmol/L (range 1.6-3.7); ($p < .0001$).

Also significantly high CSF lactate in bacterial compared to viral meningitis (mean 16.51 ± 6.1 vs 2.36 ± 0.6 mmol/L), has been reported by the earlier investigators.[74]

A systematic review and meta-analysis by Huy and colleagues which included data of 25 studies, concluded that, CSF lactate is a good single indicator and a better marker to differentiate bacterial meningitis from aseptic meningitis.[6]

Smith et al have reported, CSF lactate as a useful tool in the early diagnosis of bacterial meningitis with high sensitivity (92%) and specificity (99%) as well as in differentiating bacterial from viral meningitis.[75]

Genton B et al have endorsed the idea that the measurement of the CSF lactate is worth performing when meningitis is suspected, as it appeared to be the best way of distinguishing bacterial from non bacterial meningitis and it has highest sensitivity, specificity and predictive value.[76]

Klein et al have also reported that the CSF lactate level has higher reliability than the other CSF tests in diagnosing and differentiating bacterial meningitis from viral meningitis.[77]

Overall the present study showed that, CSF lactate concentration is a useful parameter to differentiate bacterial from viral meningitis.

In contrast to the findings of the present study, Robert et al.[78] in their study suggested that the lactate level in the cerebrospinal fluid did not provide unequivocal evidence of bacterial infection and did not gave assistance to any greater degree than the standard parameters of leukocyte count, protein and glucose contents in the differential diagnosis of bacterial meningitis from that of any other etiology.

Similarly Prasad K. and Sahu JK.[79] in 2011 commented that CSF lactate level does not hold marked advantage over conventional CSF markers in differentiating Tubercular meningitis from aseptic meningitis.

Cerebrospinal fluid (CSF) lactate assay has been a subject of research since 1925. A systematic review by Huy and colleagues[6] in the previous issue of *Critical Care* summarizes data from 25 studies evaluating the role of CSF lactate in the differential diagnosis between acute bacterial and aseptic meningitis. The authors concluded that CSF lactate is a good single indicator and a better marker compared with conventional markers. But concerns remain because of poor quality of included

studies, lack of proper 'gold standard', and limited applicability. More studies with a rigorous design are needed to determine definitively whether CSF lactate assay is a reliable and valid marker to distinguish between acute bacterial meningitis and aseptic meningitis.

It is reported that, in patients with bacterial meningitis, a complete blood count (CBC) with differential will demonstrate polymorphonuclear leukocytosis with a left shift.[32] This prompted us to sought evaluation of the blood parameters in different type of meningitis. However, no statistically significant difference was noted with respect to mean TLC in tubercular (11620 ±4229.40 cells/m^3), viral (15832.73±2943.91 cells/m^3), pyogenic (13807.69 ± 16207.38 cells/m^3) and Cryptococcal (8600 ± 4156.92 cells/m^3) meningitis ($p>0.050$). However, mean ESR was significantly elevated in patients with tubercular meningitis (61.30± 21.95 cells/m^3) compared to viral (29.55 ± 24.26 cells/m^3) pyogenic (14.31 ± 9.62 cells/m^3) and cryptococcal (13.33 ± 2.89 cells/m^3) ($p<0.001$). These findings suggest that raised ESR levels are significantly raised in patients with tubercular meningitis.

Abro AH et al.[64] in UAE reported that, the CSF proteins and cell count (predominantly polymorphs) were high in bacterial meningitis, whereas, CSF glucose was high in viral meningitis. Earlier studies show that, in adult meningitis patients with a negative direct CSF examination, CSF lactate concentrations appear to be the most highly discriminative parameter for differentiating Bacterial meningitis from Viral Meningitis.[80]

In this study means with regard to CSF parameters, it was observed that, the mean TC levels were significantly high in patients with pyogenic meningitis

(1220.00±322.54) compared to Tubercular (443.10±197.43), cryptococcal (126.00±66.84) and viral (41.88±101.34) ($p<0.001$). Also the mean PMN levels were significantly high in pyogenic meningitis (90.00±3.87) compared to Tubercular (23.82±26.90), cryptococcal (16.67±20.21) and viral (12.12±15.57) ($p<0.001$). The mean Lymphocyte levels were significantly high in patients with viral meningitis (87.88±15.57) compared to tubercular (76.17±26.90), pyogenic (10.00±3.87) and cryptovcoccal (83.33±20.21) ($p<0.001$). The mean glucose levels were significantly high in patients with viral meningitis (65.73±13.54) compared to tubercular (56.64±19.64), cryptococcal (59.00±18.19) and pyogenic (29.55±16.53) ($p<0.001$). The mean CSF proteins were significantly high in pyogenic meningitis (267.82 ± 215.67) compared to cryptococal (213.93±27.85) tubercular (132.42±109.39) and viral meningitis (53.39±19.72) ($p<0.001$). Overall the present study showed significantly raised CSF TC, PMN and lactate levels in patients with pyogenic meningitis while CSF lymphocyte and glucose were raised in patients with viral meningitis whereas CSF protein was raised in patients with cryptococcal meningitis.

The level of CSF lactate has been considered to be an important prognostic factor to predict the outcome of bacterial meningitis and perhaps the most interesting data obtained from this study was the level of CSF lactate. The mean lactate level in the CSF of our patients with pyogenic meningitis was 12.75 ± 3.46 which is a quite high value than reported by the other investigators such as by Imuekehme et al.[81] However this study[81] was conducted under the paediatric setting. In the present study majority of the patients improved (91.43%) while 8.57% of the patients expired. Though mortality was high in patients with tubercular meningitis (13.33%) compared to pyogenic meningitis, this difference was statistically not significant

(p=0.192) suggesting lack of association with meningitis. Overall mortality for bacterial meningitis is reported between 5-10% and varies according to the patients age. Abro AH et al.[64] reported higher mortality rate in bacterial group as compared to viral one, 4 (7.54%) vs 1 (2.38%) which was consistent with this study.

Overall the present study showed that, CSF lactate level was significantly high in pyogenic meningitis and it can provide pertinent, rapid and reliable diagnostic information. Furthermore, CSF lactate level can also differentiate pyogenic from non pyogenic meningitis in a quick and better way. However, CSF lactate assay is not available in most centers in developing countries and rural settings. This and the fact that many patients receive antibiotics before lumbar puncture compromise the applicability of the findings. However, in the present study none of the patients reported history of prior antibiotic administration which was strength of this study. The limitation of the study was smaller sample size and it was a single centre which may not be representative of entire population hence the findings cannot be generalized. Further multicentric studies with large sample size are warranted to confirm these findings.

CONCLUSION

The present study showed that, CSF lactate level was significantly high in pyogenic meningitis. Hence it can provide pertinent, rapid and reliable diagnostic information. Furthermore, CSF lactate level can also differentiate pyogenic and from non pyogenic meningitis in a quick and better way.

SUMMARY

Meningitis is an inflammation of the protective membranes covering the brain and spinal cord, collectively known as the meninges. The desirability of avoiding unnecessary administration of antibiotics to non-infected patients, the potentially devastating consequences associated with administration of corticosteroids to patients with aseptic meningitis, and the need to establish diagnostic usefulness of CSF lactate has prompted this study.

The present one year cross-sectional study was done in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi. A total of 70 patients presenting with meningitis aged more than 18 years from January 2015 to December 2015 were studied. The salient findings of the study are as summarized below.

- Most of the patients were males (68.57%) and male to female ratio was 2:1.
- Age ranged from 18 to 88 years. The mean age was 46.51 ± 18.90 years. Most of the patients were aged between 18 to 40 years (42.85%) followed by 41 to 60 years (32.86%) and > 60 years (24.29%).
- Most common clinical presentation was fever noted in 97.14%. The other common presentations were headache (87.14%) and Vomiting (72.85%).
- Presence of meningeal signs was noted in 74.29% of the patients while altered sensorium was noted in 44.29% of the patients while neurological deficits were noted in 11.43% of the patients.

- Most of the patients has tubercular meningitis (42.86%) followed by viral (37.14%), pyogenic (15.71%) and cryptococcal (4.29%).

- Majority of the patients had CSF lactate levels of ≤5 mmol/L (78.57%) while lactate levels of 6 to 10 mmol/L, 11 to 15mmol/L and 16 to 20 mmol/L were noted in 8.57%, 8.57% and 4.29% of the patients respectively. The mean CSF lactate levels were 4.66 ± 4.07 mmol/L and median levels were 2.70 mmol/L with range 1 mmol/L being minimum and 16.10 mmol/L being maximum.

- It was observed that, significantly higher number of patients had raised CSF lactate levels in pyogenic meningitis ($p<0.001$).

- The mean CSF lactate levels were significantly high in patients with pyogenic meningitis (12.75 ± 3.46 mmol/L) compared to tubercular (4.11 ± 1.65 mmol/L), cryptococcal (2.93 ± 1.10 mmol/L) and viral (1.98 ± 0.40 mmol/L) ($p<0.001$).

- It was noted that TC was comparable in different types of meningitis but ESR was significantly high in patients with tubercular meningitis ($p<0.001$).

- All the CSF variables including TC, PMN, Lymphocyte, glucose, proteins varied significantly in different diagnosis ($p<0.001$).

- Majority of the patients improved (91.43%) while 8.57% of the patients expired.

- Mortality was high in patients with tubercular meningitis (13.33%) compared to pyogenic meningitis but statistically this difference was not significant (p=0.192).

Overall, CSF lactate level was significantly high in pyogenic meningitis and it can provide pertinent, rapid and reliable diagnostic information. Furthermore, CSF lactate level can also differentiate pyogenic andfrom non pyogenic meningitis in a quick and better way.

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ANNEXURE I – CONSENT FORM

"ESTIMATION OF CSF LACTATE AS DIAGNOSTIC MARKER TO DIFFERENTIATE PYOGENIC MENINGITIS FROM NON- PYOGENIC MENINGITIS"

Objective and purpose of the study

This research is intended to assess CSF lactate as diagnostic marker to differentiate pyogenic from non pyogenic meningitis. The principal investigator of the study is Dr. *** ***** under the guidance of Dr. *** *****.

Introduction and Purpose of study

Meningitis is inflammation of the thin tissue that surrounds the brain and spinal cord called meninges. CSF Lactate is a diagnostic marker which helps to differentiate pyogenic from non-pyogenic meningitis. It is low cost and faster method of diagnosing meningitis.

Procedure

If you agree to be part of the research study you will be asked about the history and will be subjected to clinical examination and blood and CSF investigations by phlebotomy and lumbar puncture.

Risk and Benefits:

The risk and discomfort you might get is while taking CSF for the investigations by lumbar puncture are pain at site of spinal tap while drawing CSF. It may post lumbar puncture headache and herniation in case of raised intracranial pressure.

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.

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

Voluntary participation/ withdrawal

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

.**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, Belagavi as part of requirement towards the completion of MD degree, review and publishing. If you have any questions regarding the study as a participant you may call.

DR. ** ****** .**
Investigator,
Post Graduate in Medicine,
Jawaharlal Nehru Medical College,
Belagavi - 590 010
Phone No.: *********

DR. ** *******$_{MD}$,**
Professor,
Department of Medicine,
Jawaharlal Nehru Medical College,
Nehru Nagar,
Belagavi – 590 010
Phone no: **********

Dr. * ******
Professor & HOD,
Department of Medicine,
Jawaharlal Nehru Medical College,
Belagavi – 590 010
Phone No: *********,
Extn: ****/****

If you have any questions about your rights as a participant you may call.

DR. ** *****,**
Chairman,
Jawaharlal Nehru Medical College Ethical Committee for Human Research,
Professor and Head, Department of Pathology
Jawaharlal Nehru Medical College
Belagavi – 590 010
Phone number: **** ******.
Extn: ****

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.

Participant's Name :

Signature/ Left Thumb Impression of the participant's :

Witness's Name :

Signature/ Left Thumb Impression. :
Investigators name and Signature :

Date :

Place :

ANNEXURE II- PROFORMA

"ESTIMATION OF CSF LACTATE AS DIAGNOSTIC MARKER TO DIFFERENTIATE PYOGENIC MENINGITIS FROM NON- PYOGENIC MENINGITIS"

Name :

In Patient number :

Occupation :

Address :

Diagnosis :

History of present illness

Past history

Tuberculosis :

Diabetes :

Hypertension :

Others :

Family history

Tuberculosis :

Physical examination

Built :

Nourishment :

Lymphadenopathy :

Vital signs

Pulse rate :

Blood Pressure:

Temperature :

Systemic examination

Sensorium :

Examination of cranial nerves :

Motor system

	Upper limb		Lower limb	
	Right	Left	Right	Left
Tone :				
Power :				
Abnormal movements :				

Sensory system

	Right	Left
Reflexes		
Triceps :		
Biceps :		
Supinator :		
Knee :		
Ankle :		
Plantars :		
Right :		
Left :		

Signs of meningeal irritation

Neck rigidity :

Kernig's sign :

Brudzinski's sign :

Spine	:
Respiratory system	:
Cardiovascular system	:
Per abdomen	:

ANNEXURE III – KEY TO MASTER CHART

-	-	Absent
+	-	Present
ADA	-	Adenosine deaminase
AFB	-	Acid fast bacilli
CSF	-	Cerebrospinal fluid
ESR	-	Erythrocyte sedimentation rate
HIV	-	Human immunodeficiency virus
PMN	-	Polymorphonuclear leukocytes
TC	-	Total count