ROLE OF CEREBROSPINAL FLUID LEVELS OF HIGHLY SENSITIVE C-REACTIVE PROTEIN AND LACTATE IN ACUTE MENINGITIS

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CERTIFICATE

This is to certify that the dissertation entitled **"ROLE OF CEREBROSPINAL FLUID LEVELS OF HIGHLY SENSITIVE C-REACTIVE PROTEIN AND LACTATE IN ACUTE MENINGITIS "** is a bonafide work done by **Dr.SAKTHIVEL. R**, at Madras Medical College, Chennai in partial fulfillment of the university rules and regulations for award of M.D., Degree in General Medicine (Branch-I) under my guidance and supervision during the academic year 2010 -2013.

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DECLARATION

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ABBREVIATIONS

µl	Microliter
ADH	Anti diuretic hormone
AFB	Acid fast bacilli
CIE	Counter Immuno Electrophoresis
CMV	Cytomegalovirus
CNS	Central Nervous System
COX	Cyclooxygenase
CSF	Cerebro spinal fluid
CT	Computerised Tomography
dl	Deciliter
DNA	Deoxr ribo nucleic acid
HIV	Human Immunodeficiency virus
hsCRP	Highly sensitive C Reactive Protein
HSV	Herpes simplex virus
ICP	Intracranial Pressure

ICSOL	**Intracranial space occupying lesion**
ICT	**Intracranial Tension**
IL	**Interleukins**
JE	**Japanese Encephalitis**
Kda	**Kilo Dalton**
LA	**Lactic Acid**
LCMV	**Lymphocytic Choriomeningitis Virus**
MCA	**Middle cerebral artery**
mg	**Milligrams**
MRI	**Magnetic Resonance Imaging**
MW	**Molecular weight**
PCR	**Polymerase chain reaction**
PMN	**Polymorphonuclear neutrophils**
RBC	**Red blood cell**
SAH	**Sub arachnoid hemorrhage**
SDE	**Subdural empyema**

TB	**Tuberculosis**
TBM	**Tuberculous meningitis**
TNF	**Tumour Necrosis Factor**
VZV	**Varicella Zoster Virus**
WNV	**West Nile Virus**

INTRODUCTION

The salutary effect of the advent of highly effective antimicrobials is represented by the available history of pyogenic meningitis since the early 18th century till date. The prognosis of the patients with bacterial meningitis in those times was dismal.

In 1920, 77 children died due to Hemophilus influenza in the Boston hospital and the outcome of Pneumococcal meningitis was equally bad, which killed as many as 300 patients. In early 1900, the mortality rate associated with meningococci was 85%.

Given its dire consequences, the prompt diagnosis and the timely identification of the species causing meningitis is crucial, which is challenged by the various confounding factors that influence the accuracy of CSF results.

The lumbar puncture is the indispensable part of the management of acute meningitis which should not be delayed unless absolute contraindications exist.

The currently used conventional methods for differentiation of the various types of meningitis have serious limitations. CSF gram stain is often not contributory and also operator dependent. It is not reliable if the organisms

are scarce in the spinal fluid or if the therapy has been started. The CSF culture often need a day or two and even longer or comes negative in partially treated cases. According to various Indian workers the sensitivity of the CSF culture is 30-60%. Therefore the treatment of meningitis, most of the time is presumptive.

The glucose value in CSF is difficult to interpret since it is influenced by the plasma glucose level in the circulation, as hyperglycemia falsely increases the CSF glucose concentration even in bacterial meningitis and hypoglycaemia is associated with low glucose level in CSF. This issue can be addressed by concurrent sampling of blood for plasma glucose along with lumbar puncture and the CSF/serum glucose ratio is used, which is highly diagnostic of bacterial meningitis if it is below 0.4.[1]

But certain other infections associated with hypoglycorrhachia are tuberculosis, fungal, parameningeal infection and brain abscess with rupture into ventricular space.[2]

Partially treated patients with use of inappropriate antibiotics can obscure the cytological and biochemical status of the spinal fluid and the chance of recovery of organisms from the spinal fluid will also become less likely. They also simulate the CSF picture of viral meningoencephalitis.

In Enteroviral meningitis, the polymorphs can flood the CSF in first 6 hours along with normal CSF glucose. In immunosuppressed patients, the mounting of CSF inflammatory response is suboptimal and can also simulate the viral picture.

Hence a quick and reliable method for differentiating the bacterial and viral meningitis is essential for optimal management outcome.

Reliable, cost effective, rapid screening tests which can be performed in any standard pathology laboratory could be of help in the differentiation of various types of meningitis in adults.

The C-reactive protein is an acute phase reactant and is a globulin chiefly produced by hepatocytes in response to various stimuli such as infection, malignancy and tissue necrosis.[42] It was discovered by Tillet[48] of France in 1931. The CRP production is also induced locally by lipopolysacharide S of gram negative bacilli in neurons and various other extrahepatic sites.[43]

Przylalkowski et al found out that the CSF CRP levels is elevated in pyogenic meningitis significantly when compared to non-pyogenic meningitis. Vaishnavi et al[69] and Tankhiwale[70] et al agreed with this observation. Gojan Raj[42] et al observed that the CSF CRP level is significantly elevated in gram negative bacillary meningitis when compared to gram positive ones.

Hence the use of CSF hsCRP latex immunoassay will rapidly differentiate the bacterial and the viral meningitis and thereby guide the management with confidence.

Apart from CSF hsCRP, the CSF lactic acid is considered as a good biomarker to differentiate between the pyogenic and the viral meningitis.[55]

The mechanism of lactate production in brain is due to the meningitis associated cerebral ischemia and anaerobic metabolism. Unlike glucose, the blood lactate level will not influence the CSF lactate level and they are largely independent of each other since the CSF lactate level depends upon the local production in the brain. This is an advantage over the CSF glucose.[54,55]

CSF lactate is highly useful in the diagnosis of post surgical meningitis which is not accompanied by specific cells and proteins.[50]

The diagnostic value of CSF lactate lies in the identification of untreated and partially treated bacterial meningitis. Intermediate levels of lactate is seen in the partially treated cases. The decrease in the lactate level is suggestive of a effective therapy and resolution of infection. The importance of CSF lactate level lies in its prognostic value in predicting the outcome of the patient.[65]

Hence we have undertaken this study to determine the usefulness of CSF hsCRP and lactate in the differentiation of viral and bacterial meningitis.

AIM OF THE STUDY

To evaluate the utility of highly sensitive c-reactive protein and lactate levels in CSF as rapid screening test to differentiate pyogenic and non-pyogenic meningitis.

REVIEW OF LITERATURE

INTRODUCTION

Acute infections of the nervous system are life endangered problems in medicine because prompt recognition, appropriate clinical judgement, and early initiation of treatment can be lifesaving.[1]

Meningitis is the inflammation of the meninges - the pia and the arachnoid of the brain/the spinal cord. When it involves the parenchymal substance of brain or spinal cord, it is called as encephalitis and myelitis respectively. Meningoencephalitis or encephalomyelitis is a more diffuse form of the disease.[2]

The distinct clinical manifestations of CNS infections include acute pyogenic meningitis, aseptic or viral meningitis, encephalitis, focal processes such as brain abscess and subdural empyema, and infectious thrombophlebitis.[2] Out of these, pyogenic meningitis is still an emergent problem especially in many developing countries; considering its dire consequences, its acute and accurate diagnosis has become a priority for clinicians.[3]

Each may manifest with nonspecific symptoms of fever and headache, which in a previously normal individual may initially be considered to be benign, until

(with the exception of viral meningitis) altered sensorium, focal deficit, or convulsions appear.[1]

HISTORY

Infections of the central nervous system is not always without serious consequences. In the early 18th century, Vieusseux described about the cerebrospinal fever epidemic in America and it was found out to be due to meningococci.[5]

Hippocrates realised the existence of meningitis and the pre-renaissance physicians such as Avicenna was aware of meningism. The description for tuberculous meningitis was 'dropsy in the brain' and it was coined by Sir Robert in 1770 but its association with tubercle bacilli was not found out until next century. The first major outbreak happened in 1810 in Geneva and reported in 1840 in Africa. Reports of outbreak came later from the Europe and the United States. African epidemics became stronger in the 20th century sweeping Nigeria and Ghana.[6]

EPIDEMIOLOGY

The exact incidence of meningitis is unknown, eventhough it is a notifiable disease. The incidence of acute pyogenic meningitis in western population is

around 2 people per 100,000 in a year. The viral meningitis is still more commoner; population based studies show incidence of 10.9 per 100,000 and the disease is more common in summer.[6]

The epidemics of meningococcal disease occur in the places where the people gather such as army barracks, college campuses and the annual Haj pilgrimage. Several factors associated with the development of the epidemics have been elucidated. The factors are immunological predisposition, demographic conditions such as population migration, socioeconomic factors like overcrowding and unhealthy living environment, climatic conditions and concurrent infections.[5,6]

The various causes of bacterial meningitis differ in their local distribution. Group B and C are most prevalent in western countries. Group A is seen in Asia and continues to predominate in Africa where it has caused major epidemics; causing about 90% of documented meningococcal meningitis cases reported.[5,6]

India is a semitropical country and the hardy bacteriae such as S. aureus and gram negative bacilli grow, and the relatively fragile bacteriae H. infl uenzae, N. meningitidis, S.pneumoniae, S.agalactiae and Listeria monocytogenes in comparison do not have a survival advantage.[4]

Low socio-economic population living in poor hygiene and low birth weight associated with malnutrition is a fertile area for the less common Streptococcus species to cause meningitis. Most of the patients go to local practitioners first which causes culture negativity and the lower isolation of H. influenzae, N.meningitidis, S.pneumoniae, S.agalactiae and Listeria monocytogenes that have not got significant resistance to the usual antimicrobials. [4]

These results highlight the very different etiological profile in India in comparison to that of the West, pointing to the fact that Asian epidemiology is distinctly different from the West.[4]

According to Infectious Disease Regulations S.I. No. 707/2003 - Infectious Diseases (Amendment) (No. 3) Regulations 2003 clinicians and laboratory directors should notify the Medical Officer of Health (MOH) immediately upon suspicion that a patient has meningitis or meningococcal septicaemia. Meningitis caused by other organisms is also notifiable as soon as possible.[4]

AETIOPATHOGENESIS AND PATHOLOGY

The Bacterial Meningitis

Pyogenic meningitis is an acute purulent infection in the sub-arachnoid space. It accompanies a CNS inflammatory response that culminates in depressed level of consciousness, convulsions, increased intracranial tension (ICT), and stroke. Meninges, Subarachnoid space, and Parenchyma are often involved in the disease process[1].

The most common organisms causing community-acquired pyogenic meningitis are pneumococci (50%), meningococci (25%), group B streptococci (15%), and Listeria monocytogenes (10%) and Haemophilus influenzae type b (<10%). N.meningitidis causes recurring epidemics of meningitis every 8 to 12 years.[1]

A surge in the bacterial meningitis of 40% is noted in large urban hospitals due to nosocomial infection.[7]

The surge in the gram negative bacillary meningitis and the concomitant decline in the S.pneumoniae meningitis can be attributed to the increase in the relative frequency of health care associated meningitis.[7]

Gram-negative bacilli are the common causatives in single episode and recurrent health care associated meningitis[8]. Escherichia coli and Klebsiella account for half of all events of nosocomial gram negative bacillary meningitis.[8]

Pathways of meningeal invasion are as follows: (a) Hematogenous (bacteremia or metastasis from elsewhere, e.g., heart, lung); (b) propagation from nearby septic focus (e.g., sinusitis, brain abscess); (c) discontinuation in skull (e.g., compound fractures, neurosurgery).[2]

The neurotropic potential of the common meningeal pathogens is related to their ability to evade the host defense mechanisms.[9] A successful meningeal pathogen is the one which will sequentially with ease, colonise the host epithelium, enter the intravascular space by evading the host defense mechanisms, breach the blood brain barrier and survive in the subarachnoid space.[9]

The three usual meningeal pathogens are the normal residents of the nasopharynx in a significant part of the population. With the antiphagocytic capsular or surface antigens they survive in the tissues of the infected host.[1]

To attach and invade through the epithelial layer, a bacterium must evade the secretory IgA and the nasopharyngeal ciliary mechanisms, attach to the apical membrane and cross to the basolateral membrane.[9]

Antecedent viral infections of the upper respiratory tract or infections of the lung as in streptococcal pneumonia predisposes the colonized patient to invasion of the blood stream.[2]

Once blood-borne, these organisms have predilection for the meninges, although the reasons for this meningeal tropism are not known.[2]

Then the bacteria must enter and survive in the intravascular space by evading the circulating complement components-mainly the alternative pathway. The capsular polysaccharide of pneumococci, the polyribosyl phosphate of H.influenzae and the capsular sialic acid of meningococci help to evade the complements causing the primary bacteremia.[10-14]

The least knowledge exists in the mechanism of penetration of blood brain barrier. Possible mechanisms are effective piliation as in the strains of E.coli causing neonatal meningitis that possess S fimbriae.[15]

Damage of the blood–CSF barrier by trauma, circulating endotoxins, or an antecedent viral infection of the meninges facilitate the entry of bacteria into the sub arachnoid space[2].

Once the bacterium enters the CSF, its survival and replication is promoted by the deficient complement and opsonic activity and the immunoglobulin concentration is not increased even after the damage to the blood brain

barrier.[16,17]The proximate effect of bacilli in the subarachnoid region results in an an inflammatory response in the pia and arachnoid as well as in the cerebrospinal fluid (CSF)[2].

Regardless of the causative organisms, there is a uniform pattern of injury. The possible and putative inflammatory mediators in the cerebrospinal fluid are TNF- alpha and IL-1,6 which causes the dose dependent and time dependent damage to the blood brain barrier preceding the clinical manifestations. [18]

The immediate response to bacteria or their toxins is increased blood flow in the meningeal venules and capillaries and vessel leak followed shortly by exudation of protein and neutrophils into the pia and subarachnoid space. Shortly, lymphocytes and histiocytes invade gradually in relative and absolute numbers. During this time fibrinogen is converted to fibrin after a few days. This is followed by plasma cell recruitment. [2]

The organization of the exudate, causing the fibrosis of the arachnoid and loculation of pockets of exudates then occur.[2]

As the disease becomes established, the pia-arachnoid exudate collects in the base of the brain (basilar meningitis), impeding the flow of CSF which results in hydrocephalus. The exudate organise around cranial nerves and lead to focal neuropathies.[2]

Intracranial pressure is often increased in patients with pyogenic meningitis and is associated with the cerebral herniation.[19]

Because of the rigid confine of skull and spine, intracranial pressure is often related to the volume of the substance, the cerebrospinal fluid and the blood flow. Accordingly brain swelling due to the cerebral edema, the hydrocephalus or the increase in blood flow cause increase in the intracranial pressure. [19]

Various therapeutic targets based on the pathophysiology of meningitis is as follows. Bacteriolysis and the release of bacterial components into CSF is prevented by the use of bactericidal antibiotics with less bacteriolysis. Local generation of inflammatory mediators like TNF-alpha, interleukins into CSF is prevented by steroids and pentoxifylline.[20-22] Cytokines induced recruitment of PMNs is prevented by steroids, cytokine antagonists and monoclonal antibodies to adhesion glycoprotein[23]. Activation of CSF neutrophils and release of vasoactive mediators that breach the blood brain barrier is targeted by steroids, COX inhibitors[24], antagonists of platelet activating factor.

Recurrent Bacterial Meningitis

Recurrent Bacterial Meningitis is seen often in the ventriculovenous shunting procedure for the treatment of hydrocephalus or who have a partially closed dural opening.[2]

A congenital neuroectodermal sinus or a fistulous connection between the nasal sinuses and the subarachnoid space is to be considered in unresolving cases. More often the fistula in these patients is a result of a previous basilar skull fracture.[2]

The CSF leaks is most commonly seen in patients with recurrent meningitis either community acquired or health care associated.[2]

The site of trauma is in the frontal or ethmoid sinuses or the cribriform plate, and S.pneumoniae is the usual pathogen. Often it reflects the predominance of such strains in nasal carriers. These cases usually have a good prognosis; mortality is much lower than in ordinary cases of pneumococcal meningitis.[2]

Brain abscess

Brain abscess is usually caused by a metastatic infective focus elsewhere. In 10% of the patients, it results from compound fractures, intracranial operations etc.[1] Disease of parameningeal spaces accounts for 40% of all cases.[2]

Most common Sinuses implicated are the frontal and sphenoid and infections from here usually go to frontal and temporal lobes respectively. Foci from heart and lung are commonly encountered in modern era.[2]

Most common areas of brain involved are anterolateral cerebellar hemisphere and middle and inferior temporal lobe.[1]

Subdural empyema

A subdural empyema[1] (SDE) is an accumulation of pus in the subdural space. Sinusitis is the common predisposing culprit and typically involves the frontal sinuses, either alone or in combination with the ethmoid and maxillary sinuses. Sinusitis associated empyema has a striking predilection for young males, possibly reflecting sex-related differences in sinus anatomy and development.[1]

Aerobic and anaerobic streptococci, staphylococci, Enterobacteriaceae, and anaerobes are the usual pathogen of sinusitis-associated SDE.[1]

Cranial epidural abscess

A cranial epidural abscess occurs as a result of a cranial surgery complication or complicated fracture of cranium or as a result of spread of infection from the mastoid, tympanum and frontal sinuses or orbit. It may develop contiguous to an area of osteomyelitis, when wound infection occurs following craniotomy[1].

Staphylococci or gram-negative organisms are the most common causes in patients with craniotomy or compound skull fracture.[1]

Viral Infections of the CNS

The most noted agents of acute viral meningitis are enteroviruses (including echoviruses and coxsackieviruses in addition to numbered enteroviruses), HSV type 2, HIV, and arboviruses.[2]

The family of herpesviridae most commonly causes sporadic cases in immune population. Arboviruses which include various taxonomic groups such as alphaviruses, flaviviruses(JE Virus) and Bunyaviruses cause encephalitis epidemics.[2]

Mumps, measles, and VZV follow the respiratory passages. Polioviruses and other enteroviruses enter by the oral–intestinal route, and HSV enters mainly via the oral or genital mucosal route. Other viruses are acquired by inoculation, as a result of the bites of animals (e.g., rabies) or mosquitoes (arthropod-borne or arbovirus infections). The fetus may be infected transplacentally by rubella virus, CMV, and HIV[2,25].

Following entry into the body, the virus multiplies locally and in secondary sites and usually gives rise to a viremia. Viruses cross into the nervous system both within migrating lymphocytes and directly through areas of glial and vascular regions that are permeable to the organisms [2,25].

Another pathway of infection is along peripheral nerves; centripetal movement of virus is accomplished by the retrograde axoplasmic transport system. HSV, VZV, and rabies virus utilize this peripheral nerve pathway[2,25].

Tuberculous meningitis

Arnold and Howard showed that meninges cannot be involved directly through blood stream by tubercle bacilli and there is a definite foci in the meninges and subcortex from which tubercle bacilli enters the subarachnoid space[26,27].

Later a dense gelatinous exudate forms in the subarachnoid space and is most exuberant in the interpeduncular and sellar areas and also extends to the cisterna prepontis and around the spinal cord[26-27].They rim the vessels and cranial nerves and obstruct the flow of CSF causing hydrocephalus[26-27].

The most devastating sequelae is the development of vasculitis involving the major vessels, the posterior circulatory system and the perforators of MCA. The parenchyma is damaged as a result of hard exudates owing to its close contact with the substance, possibly due to hypersensitivity phenomenon.[26-27]

Clinical manifestations of meningitis

Fever, intense headache, and the neck stiffness(resistance to passive movement on forward bending) often accompanies generalized seizures and a depressed mentation progressing to coma[28].

Brudzinski sign and Kernig sign have the same importance as stiff neck but are less often reproducible[2,28,29].

Meningococcal meningitis should be suspected when the evolution is extremely rapid (delirium and stupor may supervene in a matter of hours), when the onset is attended by a petechial or purpuric rash or by large ecchymoses and lividity of the skin of the lower parts of the body, when there is circulatory shock, and especially during local outbreaks of meningitis. Because a petechial rash accompanies approximately 50 percent of meningococcal infections, its presence dictates immediate institution of antibiotic therapy[30].

Pneumococcal meningitis is often preceded by an infection in the lungs, ears, sinuses, or heart valves. In addition, a pneumococcal etiology should be suspected in alcoholics, in splenectomized patients, in the very elderly, and in those with recurrent bacterial meningitis, dermal sinus tracts, sickle cell anemia ("autosplenectomized"), and basilar skull fracture[31].

On the other hand, H. influenzae meningitis usually follows upper respiratory and ear infections in the child[32].

Meningitis in the presence of furunculosis or following a neurosurgical procedure should direct attention to the possibility of a coagulase-positive staphylococcal infection. Ventricular shunts inserted for the control of hydrocephalus are particularly prone to infection with coagulase-negative staphylococci[32].

HIV infection, myeloproliferative or lymphoproliferative disorders, defects in cranial bones (tumor, osteomyelitis), collagen diseases, metastatic cancer, and therapy with immunosuppressive agents are clinical conditions that favor invasion by such pathogens as Enterobacteriaceae, Listeria, A.calcoaceticus, Pseudomonas, and occasionally by parasites.[33]

Seizures are encountered most often with H. influenzae meningitis[34].

Cranial nerve abnormalities are particularly frequent with pneumococcal meningitis, the result of invasion of the nerve by purulent exudate and possibly due to ischemic damage as the nerve traverses the subarachnoid space[32-34].

Listeria infection may take the form of a brainstem encephalitis, or "rhombencephalitis," specifically with several days of headache, fever, nausea,

and vomiting followed by asymmetrical cranial-nerve palsies, signs of cerebellar dysfunction, hemiparesis, quadriparesis, or sensory loss. Respiratory failure has been reported.[34]

A brain abscess usually features as an expanding space occupying lesion with extremely variable evolution of symptoms and signs[1].

The classic clinical triad of Brain abscess is headache, fever, and a focal neurologic deficit which is present in <50% of cases[1].

A patient with Subdural empyema (SDE) usually comes with fever and worsening headache. The diagnosis of SDE should always be suspected in a patient with known sinusitis who presents with new CNS signs or symptoms. As the infection progresses, focal neurologic deficits, seizures, nuchal rigidity, and signs of increased ICP commonly occur[1].

Cranial epidural abscess presents with fever (60%), headache (40%), nuchal rigidity (35%), seizures (10%), and focal deficits (5%). Development of symptoms may be insidious. Periorbital edema and Potts puffy tumor, reflecting underlying associated frontal bone osteomyelitis, are present in 40%.[1]

This diagnosis should be considered when fever and headache follow recent head trauma or occur in the setting of frontal sinusitis, mastoiditis, or otitis media[1].

In tuberculous meningitis the early manifestations are usually low-grade fever, malaise, headache (more than 50 percent of cases), slow mentation, confusion, and neck rigidity (75 percent of cases), with Kernig and Brudzinski signs. Characteristically, these symptoms evolve less rapidly in tuberculous meningitis[26-27].

The seeding of tuberculous bacilli into CSF heralds the insidious clinical picture comprising of gradually fluctuating fever onset, weight loss, headache, behaviour changes and vomiting. Interventional delay lead on to neurological deficits, loss of consciousness, seizures and it is the most common point of time when the diagnosis is considered[26-27].

Signs of cranial nerve involvement (usually ocular palsies, less-often facial palsies or deafness) and papilledema may be present in TB Meningitis[26-27].

Evidence of active tuberculosis elsewhere, usually in the lungs and occasionally in the small bowel, bone, kidney, or ear is seen in 60% of cases[26,27].

Usually the onset is acute and the temperature is elevated, from 38 to 40°C (100.4 to 104°F). Headache that is more severe than that associated with other febrile states is the most frequent symptom. A variable degree of lethargy, irritability, and drowsiness may occur; confusion, stupor, coma, and seizure mark the case as encephalitis rather than meningitis[1,2].

Immunocompetent patients with viral meningitis usually present with headache, fever, and signs of meningeal irritation. Headache is almost always present and often characterized as frontal or retroorbital. Patients frequently complain of photophobia and pain on moving the eyes. Neck stiffness is present in most cases but may be mild and present only near the limit of neck anteflexion. Patients often have constitutional symptoms and signs like malaise, myalgia, anorexia, nausea and vomiting, abdominal pain, and/or diarrhea. Patients also can be mild lethargic or drowsy; however, profound alterations in consciousness, such as stupor, coma, or marked confusion do not occur in viral meningitis. Similarly, seizures or focal neurologic signs or symptoms or neuroimaging abnormalities indicative of brain parenchymal involvement are not typical of viral meningitis and suggest the presence of encephalitis or another CNS infectious or inflammatory process.[1,2]

The symptoms of acute HSV encephalitis are fever, headache, seizures, confusion, stupor, and coma. In some patients these manifestations are

preceded by symptoms and findings that betray the predilection of this disease for the inferomedial portions of the frontal and temporal lobes.[2]

Hallucinations of smell and taste, temporal lobe seizures, behavioural or personality abnormalities, cortical function impairment like aphasia and hemiplegia are also present[2,3].

Swelling and herniation of one or both temporal lobes through the tentorial opening may occur, leading to coma during the first few days of the illness, a very poor prognostic sign[2,3].

DIAGNOSIS

Bacterial meningitis

When meningitis is suspected, blood culture is taken without delay and empirical antibiotics and adjunctive steroids are administered promptly. Cerebrospinal fluid is tapped for analysis to diagnose the cause of meningitis.[1]

Bacteremia is not a contraindication to lumbar puncture. The dilemma concerning the risk of promoting transtentorial or cerebellar herniation by lumbar puncture, even without a cerebral mass has been settled in favor of performing the tap if there is a reasonable suspicion of meningitis. It must be pointed out that a cerebellar pressure cone (tonsillar herniation) may occur in

fulminant meningitis independent of lumbar puncture; therefore the risk of the procedure is probably even less than usually stated[2].

Only a sizable brain abscess or substantial brain swelling entirely interdicts a lumbar puncture in suspected bacterial meningitis. Furthermore, the fact that death results from cerebral herniation in many fatal cases of bacterial meningitis does not, of course, mean that lumbar puncture precipitated the demise [35-37].

The need to take neuroimaging studies before LP requires clinical judgement. Neuroimaging studies is not necessary in immune individuals with no history of prior cranial trauma and normal mentation and no neurological deficit and disc bulge on funduscopy[1].

If there is clinical evidence of a focal lesion with increased intracranial pressure, then CT or MRI scanning of the head, looking for a mass lesion, is a prudent first step, but in most cases this is not necessary and should not delay the administration of antibiotics[2].

Patients aged above 60 years, with immunocompromised state, those who had a history of neurological disorder and those who had a convulsion 1 week before are more likely to have an abnormal finding in imaging[35].

On analysing the physical findings at presentation, patients who had an altered mentation, with inability to respond to two continous commands aptly, with gaze palsy, field defects, arm and leg drift, or language dysfunction are more likely to have an abnormality in imaging[36].

When there are signs of impending herniation or indications of a dangerous configuration on cerebral images, one may wish to draw blood cultures and treat empirically rather than take the small risk of precipitation of herniation with a lumbar puncture[2]. Increased opening pressure of >180 mmH_2O is seen in 90%.

Any coagulopathy that is deemed a risk for hemorrhagic complication of lumbar puncture should be rapidly reversed if possible.[2] Platelet transfusion is considered when the disease associated with any hemorrhagic diathesis is contemplated, for example, meningococcal septicaemia. It is indicated when the platelet count goes below 20,000/μL or the count is declining rapidly.[3]

Protamine administration is considered in the patients on heparin and vitamin K/Fresh plasma infusion in patients on warfarin to prevent untoward bleeding events associated with lumbar puncture.[3]

Any infection at the local site contraindicates the lumbar puncture procedure.[1]

The opening pressure is invariably increased above 180 mm H_2O that a normal reading on the the first attempt in a patient with doubted pyogenic meningitis suggests another diagnosis or it can be due to the occlusion in the needle or block in the subarachnoid space.[2]

Patients with depressed level of consciousness have a very much elevated level of CSF opening pressure whose incidence is around 40%[35].

A pleocytosis in the CSF is diagnostic of meningitis. The number of Polymorphs is from 200 to 100,000/mm^3, but the usual one is from 10^3 to $10^{36,38}$. Count exceeding 50,000/mm^3 increase the chance of brain abscess rupturing into CSF space.

PMNs predominate (85 to 95 percent of the total), but rise in mononuclear cells is found in the partially treated meningitis[2].

Cell counts below 1000 cells/µl is found in early infection (15%), partially treated meningitis, immunosuppressed individuals, or in a nonbacterial cause. Rarely, cell counts of less than 100 cells/ µl are seen in the apurulent pneumococcal meningitis. (Felgenhauer and Kober 1985), with exuberant bacterial meningeal infection and absent PMN response in the spinal fluid[3].

Normal or slightly increased CSF cell count is encountered in upto ten percent of cases and are seen to be followed by a downhill clinical course[38]. The protein content of more than 45 mg/dl is seen in around 85% of cases; usually it lies in the range of 150 to 450 mg/dl[2,36,41].

The glucose level is invariably decreased to 40 mg/dl or less; or below 40% of blood glucose concentrations[2,36,41]

The CSF/serum glucose ratio eliminates the error that occurs due to hyperglycemia, which may increase the glucose levels in CSF. A spinal fluid/serum glucose ratio below 0.4 usually occurs in pyogenic meningitis and it is highly diagnostic.[1] It requires from half an hour to several hours for serum glucose level to equilibriate with CSF levels and therefore if we do LP early after the administration of dextrose it will not affect the CSF glucose results.[1]

Other causes of hypoglycorrachia include sarcoidosis of CNS; fungal or tuberculous meningitis, SAH, carcinomatous involvement of meninges, chemical meningitis from craniopharyngioma or teratoma and meningeal gliomatosis[2,36].

Nigrovic and colleagues established a prediction scheme that stratifies cases having a low risk for for pyogenic meningitis if they don't have these features: positive CSF Gram stain, CSF PMN count around 1,000 cells/µl, CSF protein around 80 mg/dl, peripheral PMN count of at least 10,000 cells/µl, and an

episode of convulsion on presentation. This rule has been validated in a multicenter retrospective cohort study that encompassed 3,295 patients. Of 1,714 patients who were categorized at very low risk, only 2 had bacterial meningitis.[2]

The Gram stain of the spinal fluid mostly identifies the causative agent; pneumococci and H.influenzae are identified more readily than meningococci.[2]Sensitivity is upto 60% .[1]

The most common error in reading Gram-stained smears of CSF is the misinterpretation of precipitated dye or debris as gram-positive cocci or the confusion of pneumococci with H. influenzae.[2]

CSF culture comes positive in 65 to 85 percent of cases of bacterial meningitis, are best obtained by collecting the fluid in a sterile tube and immediately inoculating plates of blood, chocolate, and MacConkey agar; tubes of thioglycolate (for anaerobes); and at least one other broth.[2]

The likelihood of finding Gram stain or culture-positive CSF may decrease to 5-40% if antibiotics were administered before the LP.

Administration of antibiotics a few hours prior to lumbar puncture will not influence the result of CSF culture when the procedure is done along with the blood cultures, latex agglutination and counter immunoelectrophoresis [38,39,41].

Because antibiotic therapy takes longer than 12 hours to sterilize CSF, culture results are often positive for the first several hours after antibiotics[41].

The problem of identifying causative organisms that cannot be cultured, particularly in patients who have received antibiotics, may be overcome by the application of several special laboratory techniques[2].

One of these is counterimmunoelectrophoresis (CIE), a sensitive test that permits the detection of bacterial antigens in the CSF in a matter of 30 to 60 min. It is particularly useful in patients with partially treated meningitis, in whom the CSF still contains bacterial antigens but no organisms on a smear or grown in culture[2,40,41].

Despite culture negativity in CSF, if we still suspect bacterial meningitis, use of sensitive diagnostic tools like polymerase chain reaction can help detect bacteria in CSF although their routine use awaits further guidelines[38-41].

Blood cultures should be obtained in all patients, since positivity of around 40 to 60 percent is seen with H. influenzae, N.meningitidis, and S.pneumoniae meningitis, and can be a sole certain pointer to the organism.[1,2,38]

Isolation of an organism is not only helpful in establishing the diagnosis, but allows the identification and susceptibility testing of the aetiological agent. The

culture result can also be used to decide on the need for antibiotic prophylaxis, contact tracing, and other public health control measures.

The spinal fluid Latex agglutination test has a specificity of 90–100% for pneumococci and meningococci. So, when the test comes positive it is highly diagnostic rather than just suggestive. However, the sensitivity of the CSF LA test is only 75–100% for detection of S. pneumoniae and 35–70% for detection of N. meningitidis antigens, so, when it comes negative it does not exclude the possibility[1,39].

The Limulus amebocyte lysate test rapidly detects the gram-negative endotoxin in spinal fluid and thereby diagnosing gram-negative bacterial meningitis. Specificity is around 80–100% and sensitivity nears 100%.[1]

Limulus amebocyte lysate test positivity is seen in almost all patients with gram-negative bacillary cases. False positives do occur.[1]

Measurements of chloride concentrations in the CSF are not very useful but they are usually found to be low, probably reflecting dehydration and low serum chloride levels. In contrast, CSF lactate dehydrogenase (LDH), although infrequently measured, can be of diagnostic and prognostic value. Levels of lactic acid in the CSF (determined by either gas chromatography or enzymatic analysis) are also elevated in both bacterial and fungal meningitides (greater

than 35 mg/dl) and may be helpful in distinguishing these disorders from viral meningitides, in which lactic acid levels remain normal.[1,2]

Viral infections

The clinical and labarotory manifestations of viral infection of the central nervous system especially HSV can simulate that of bacterial meningitis.

Viral meningoencephalitis, and particularly herpes simplex virus (HSV) encephalitis, can mimic the clinical presentation of bacterial meningitis. The typical CSF profile with viral CNS infections is a lymphocytic pleocytosis with a normal glucose concentration, in contrast to PMN pleocytosis and hypoglycorrhachia characteristic of bacterial meningitis.[1]

The typical profile is a lymphocytic pleocytosis (25–500 cells/µL), a normal or slightly elevated protein concentration [0.2–0.8 g/L (20–80 mg/dL)], a normal glucose concentration, and a normal or mildly elevated opening pressure (100–350 mmH_2O). Organisms are not seen on Gram's stain of CSF.

Immunocompromised patients due to varied etiology will not feature a florid pleocytic response in their spinal fluid.[25]

Polymorphonuclear pleocytosis occurs in 45% of patients with WNV encephalitis and is also a common feature in CMV myeloradiculitis in

immunocompromised patients. Besides one should not forget to doubt the possibility of bacterial infection including leptospires, amebic and other non infectious process such as leukoencephalitides when PMN persists in CSF.[25]

RBCs in CSF can occur in the range of 500/µL even when the tap is done without causing any trauma. The incidence is around 10%.The pathologic equivalent of this finding may be a hemorrhagic encephalitis of the type seen with HSV. The CSF contains erythrocytes or is xanthochromic in haemorrhagic encephalitides such as herpes simplex encephalitis and acute necrotic leucoencephalitis.[2.25]

Hypoglycorrhachia in viral infections is seen in mumps, LCMV, ECHO and enteroviral meningitis. The possibility of Listeria, tuberculous or fungal infection and non infectious process such as sarcoid are to be considered in lymphocytic pleocytosis with hypoglycorrhachia.[2,25]

PCR has become the diagnostic procedure of choice and is substantially more sensitive than viral cultures.[1]

Detection of intrathecal synthesis (increased CSF/serum HSV antibody ratio corrected for breakdown of the blood-brain barrier) of HSV-specific antibody may be useful in diagnosis of HSV meningitis in patients in whom only late (>1 week post-onset) CSF specimens are available and PCR studies are negative.[1]

The sensitivity of CSF cultures for the diagnosis of viral meningitis and encephalitis, in contrast to its utility in bacterial infections, is generally poor.[1]

Tuberculous meningitis

The typical CSF features in TBM are: (1) Increased opening pressure, (2) lymphocytic count (10–500 cells/µL), (3) increased protein level of 1–5 g/L, and (4) hypoglycorrhachia around 20–40 mg/dL

The protein content of the CSF is always elevated, between 100 and 200 mg/dL in most cases, but much higher if the flow of CSF is blocked around the spinal cord.[2]

The glucose falls slowly and a reduction may become manifest only several days after the patient has been admitted to the hospital. The serum sodium and chloride and CSF chloride are often reduced, in most instances because of inappropriate ADH secretion or an addisonian state because of tuberculosis of the adrenals.[2]

To demonstrate Cobweb feature or AFB on smear, sample the CSF from the last tube collected at lumbar puncture. AFB is seen very well in the clot or pellicle on the fluid surface. Sensitivity is around 10-40% for AFB smear.

It takes 4-8 weeks for culture to become positive and its sensitivity is around 50%. Culture continues to be the gold standard to make the diagnosis of TBM.[1]

PCR for the detection of M. tuberculosis DNA should be sent on CSF if available, but the sensitivity and specificity on CSF have not been defined. The Centers for Disease Control and Prevention recommend the use of nucleic acid amplification tests for the diagnosis of pulmonary tuberculosis.[1]

IMAGING IN CNS INFECTIONS

CT and MRI scans of the brain and spinal cord can be extremely useful for the diagnosis of the site, nature, and extent of mass lesions and associated oedema, sub and epidural empyemas, meningitis, cerebritis, and ventriculitis, the presence of intracranial hypertension, hydrocephalus, cerebral and brainstem herniation, demyelination, and other anatomical abnormalities.[2]

ROLE OF CSF LEVELS OF hs-CRP

The concept of C-Reactive protein and acute phase reactants was introduced by Tillette et al in 1931. The substance was found to agglutinate with the capsular polysaccharide of pneumococci which was first described in the sera of acutely ill patients. Later it was found to be a protein and given the name CRP.[42]

It was the first acute phase reactant substance discovered. It is important in the non specific host defense mechanisms and monitored as an indicator of inflammation. Its clinical utility is lies in the diagnosis of the infections, autoimmune diseases and atherosclerotic diseases. [43]

CRP belongs to the pentraxin family of calcium dependent ligand binding plasma proteins.[43]

It is composed of five homologous subunits of non-glycosylated polypeptides that are linked to each other by non-covalent bonds forming a disk shaped structure with a MW of 120 Kda. It contains little or no carbohydrates.[43]

CRP is mainly synthesised in the liver. But it is shown that CRP can also be produced in the nervous system and lipopolysaccharides of gram negative bacilli can stimulate the CRP production in nonhepatic sites.[43,44]

CRP levels are affected by factors such as hepatic dysfunction, patients on steroids and oral contraceptives, severe dyslipidemia and infections and tissue necrosis elsewhere.[42]

It is important in the innate defense mechanisms. Similar to immunoglobulins, it activates complement components, binds Fc fragment and acts as opsonins.[45]

Unlike immunoglobulins, it binds to altered self and foreign molecules with pattern recognition receptors. The ability to bind Fc receptors generate proinflammatory mediators that amplify the inflammatory response.[46]

Its main role is to scavenge or clear the apoptotic bodies and other byproducts such as deoxyribonucleic acid which are lethal and immunogenic and also participates in opsonisation that aids phagocytosis. These defense mechanisms are not adaptive one to the stimuli.[47]

CRP binds when the phospholipids are exposed as a result of damage to the lipid bilayer of the cell membrane and hence attack the affected cells only.[47]

Thus CRP acts as a surveillance molecule for altered self molecules and certain pathogens. It provides early defense response and generate proinflammatory signal and activation of humoral adaptive immune mechanisms.[48]

CRP production is apart of the non specific acute phase response to most forms of inflammation, infection and tissue damage and was therefore considered not to provide clinically useful information, indeed CRP values can never be diagnostic on their own and can only interpreted in full knowledge of all other clinical and pathological results.

In healthy young volunteer blood donors, the median CRP concentration was 0.7mg/l. The concentration in cerebrospinal fluid is six to seven fold lower than that of serum. CRP produced from liver undergoes ultrafiltration to enter the CSF. Once it enters the CSF, it binds to the damaged tissue.[48]

Meningeal irritation stimulates CRP production. Minimal CSF inflammation is seen during the early part of the disease and with the rapidly developing meningitis, the bacterial multiplication outpace the ability of the liver to mount a CRP response.[43]

Plasma half life of CRP is about 19 hours. It is constant in both the health and the disease. Therefore the sole determinant of circulating CRP concentrations is the synthesis rate. When the stimulus for increased production completely

ceases, the circulating CRP concentration falls rapidly at almost the rate of plasma CRP clearance.

CRP levels in CSF were elevated significantly in pyogenic meningitis compared to non-pyogenic meningitis. Among the pyogenic group, CSF CRP was higher in cases caused by Gram-negative organisms compared to Grampositive organisms.[49]

This signifies the relationship between CSF CRP levels and the integrity of the blood brain barrier which is more prone to greater level of damage seen in gram negative bacillary meningitis. This is due to the production of endotoxin Lipopolysaccharides-S by gram-negative bacilli.[46]

Endotoxic lipopolysaccharide of Gram negative bacilli can also stimulate the local synthesis of CRP in CSF. It is considered to be yet another reason for CSF CRP levels elevation which is more significant in gram negative cases. [46]

In pyogenic meningitis the CRP is not produced as a result of bacilli and polymorphs, only the anaerobic environment helps in the CRP production.[46]

The interplay between cytokine superfamily, polymorphs and vascular endothelial layer assumes a prominent role in the pathogenesis of damage to the blood brain barrier which occurs as a result of dehiscence of intercellular junctions and thereby resulting in the allowance of entry of CRP into CSF space.[46]

As already stated above, the CRP level in CSF is associated with the level of integrity of blood brain barrier and therefore any increase in the level of CRP is related with the progressive ongoing damage to the barrier causing increased permeability to the CRP[46].

CSF CRP levels are significantly lower in non-pyogenic meningitis group, which includes cases of tubercular meningitis, viral meningitis and fungal meningitis.[46]

When the CSF shows normal levels of glucose and protein and negativity for gram stain with low grade cell count of around 50 PMNs/µL but yet the clinical scenario is more favoring that of a viral etiology, the CRP assay will be of adjunct value, the absence of which, will guide us in the therapeutics of whether to continue antibiotics or not.[46]

The CSF-CRP is of immense help when there is no definitive evidence of infection by the various conventional methods and the finding always signifies a bacterial etiology.[46]

CRP is helpful in the disease progression in meningitis[26]. It is also elevated in various other CNS inflammatory diseases including multiple demyelination.[47-49]

ROLE OF CSF LEVELS OF LACTATE

CSF lactate is considered as a good biomarker for discriminating between pyogenic from viral meningitis[51].

The CSF Lactate concentration is directly dependent upon its production rate in the brain. There is substantial evidence, in patients and animals, that blood and CSF lactate concentrations are largely independent of each other. This is important in clinical practice because it is not necessary to collect matched plasma[50,51].

CSF lactate concentrations are also useful for the diagnosis of post surgical acute bacterial meningitis, where there is not an increase in specific cells or proteins[51,52].

CSF from patients with viral meningitis can have a predominance of neutrophils during the first 6 h of the disease, with CSF glucose concentrations and the CSF/serum glucose ratio being normal. This is more common among patients with meningoencephalitis caused by enterovirus. CSF LA showed lower concentrations in this group compared to the group with bacterial meningitis[51,53].

Increased CSF lactate is associated with low CSF glucose concentrations. While a moderate increase in lactate is often observed with normal CSF glucose, the occurrence of a very low CSF glucose concentration is usually associated with a substantial increase in lactate concentrations. This is indicative of increased anaerobic glycolysis by the adjacent cerebral tissue, or by cellular infiltrates in the leptomeninges[54-56].

CSF lactate comes from various sources in pyogenic meningitis. Bacilli can contribute, by themselves, to the local production of lactate but to a minimal level of 10%[51,56].

Neurons and Glia in nervous tissue are the main site for the production of lactate in pyogenic meningitis which occurs through various mechanisms[51,56].

Cerebral ischemia that occurs in bacterial meningitis results from generalised brain edema associated with decrement in the global cerebral perfusion and the inflammation that occurs in the vasculature which accompanies vasoconstriction and thrombo occlusion besides failure of autoregulatory mechanisms[51,56,59].

The various inflammatory mediators including cytokine superfamily alter the energy metabolism that occurs in the central nervous system which involve impairment in the tissue oxygen utilization mechanisms. Oxygen uptake system is seriously curtailed. This is a superadded insult which promotes anaerobic metabolism and as a result, the lactate production[56].

The cytokines act as chemoattractants that result in the recruitment of polymorphs in the CSF space which lead on to augmented glycolysis and lactate production in pyogenic meningitis[59].

The important implication of CSF lactate level determination in the clinical use lies in the prompt discrimination between the viral meningoencephalitis (<3 mmol/L) and pyogenic meningitis-both partially treated (>3-6 mmol/L) and untreated cases (>6mmol/L)[56].

In sporadic cases CSF lactate level determination is more sensitive than CSF/Serum glucose ratio and confirmed as a better differentiating factor between pyogenic and non pyogenic meningitis patients than that of CSF/Serum glucose ratio[59].

Partially treated pyogenic meningitis patients always present with the confounding CSF results and continues to be a diagnostic challenge. Hence this led to the kindling of interests whether CSF lactate level determination could solve this issue[59,64].

This led to the finding of intermediate level of lactate concentration in CSF of partially treated meningitis which occurred not due to chance and is attested by many studies. This also culminated in the concept of decrease in the lactate level with the adequate treatment and the subsidence of disease[59,64].

Whenever the CSF glucose is not contributing or with hypoglycorrhachia but yet the viral etiology is suspected for instance HSV-1 in some cases, CSF lactate level assay will solve the problem as lactic acid will not be elevated in viral etiologies[54,59].

The finding of minimal elevation of around 2 to 4 mmol/L is not to be confused with the pyogenic meningitis. The explanation for this mild elevation is given as the presence of RBC s in the CSF which accompanies the hemorrhagic necrosis of HSV encephalitis which may cause elevation of lactate levels but only slightly unlike pyogenic meningitis associated lactate levels[59].

The clinical course of the pyogenic meningitis patients can be known from the lactate levels. The prognostic status of the patients can be deciphered from CSF lactate level and it can predict those who are likely to recover with or without sequelae and also the risk of mortality[59,65].

A spectrum of elevation is seen in the CSF lactate levels such that higher levels is seen in patients who expired and intermediate levels seen in patients who have met sequelae. Patients with lower levels have been found to have recovered uneventfully[59,65].

Elevated CSF lactate levels is seen in other conditions such as hypoxia, SAH and head trauma[59,64].

MATERIALS AND METHODS

Study design

Cross sectional study

Setting

All patients admitted in our department of Internal medicine, Rajiv Gandhi Govt. General Hospital, with clinical syndrome suggestive of acute meningitis such as fever, headache, neck stiffness, seizures, vomiting, altered sensorium, signs of meningism and focal neurologic deficit regardless of their past treatment status are enrolled in our study.

Sample

50 patients admitted to our department of Internal medicine, Rajiv Gandhi Govt. General Hospital, with clinical syndrome suggestive of Acute meningitis such as fever, headache, neck stiffness, seizures, vomiting, altered sensorium, signs of meningism and focal neurologic deficit regardless of their past treatment status are enrolled in our study. Informed consent was obtained from the patients or the attenders if the patient is sick enough to give the consent.

Inclusion criteria

Patients with fever, headache and signs of meningeal irritation with or without seizures and depressed level of consciousness.

Exclusion criteria

Patients with contraindications for lumbar puncture like those with documented ICSOL, coagulopathy, local infection at sites of lumbar puncture, patients with pyogenic infections elsewhere with tissue necrosis and those with malignancy, those with severe hepatic failure, patients on long term steroids and OCP, patients with recent history of stroke were excluded from the study.

Procedure

A questionnaire prepared noted the duration and detail of illness. The clinical constellation of symptoms suggestive of acute meningeal infection such as fever, headache, neck stiffness, seizures, vomiting , altered sensorium and focal neurological deficit such as blindness, double vision, hemiparesis, bulbar symptoms etc. were noted. Past history of Diabetes, Tuberculosis and immunodeficient states and drug history was elicited. Personal history of smoking, alcohol abuse and substance abuse, if any, was elicited. A detailed

physical examination was conducted which included the vitals, hydration status, pulse oximetry, skin besides a thorough systemic examination. Screening neurological examination was done to document the signs of meningeal irritation and to evaluate the focal neurological deficit. Complete blood count, random blood sugar, renal and liver function test, serum electrolytes, urine routine and ECG were done. Chest x ray was done to rule out the infective foci like pneumonia, Koch's. An urgent coagulation profile was performed to rule out coagulopathy. Adequate amount of blood was sampled for culture and sensitivity emergently prior to the administration of steroids and empirical antibiotics. If there were no features coma on presentation, focal neurological deficit or immunocompromised state features, a lumbar puncture was performed without delaying unduly for imaging. The procedure was done after getting the informed consent. The patient was put in the universal flexion position with assistance and L3-L4 space was identified and lumbar puncture was done with the optimal gauge spinal needle under sterile precaution with draping. Adequate amount was sampled and its appearance was noted. The sample was sent for cell count, cytology, protein, sugar, gram stain, AFB stain, lactic acid and high sensitive CRP level, india ink preparation and PCR (if clinically indicated). Separate sample was drawn with sterile precaution in a culture broth for culture and sensitivity. Emergent CT or MRI if needed, as

dictated by clinical scenario, with contrast, was done to note the meningeal enhancement and to evaluate for the complications of meningitis. Optimal fluid therapy and nursing care were provided.

Instruments

Chest x ray: A Chest x ray posteroanterior view is done to rule out the infective foci such as Koch's, pneumonia etc.

CT/MRI with contrast +/- angiogram: To document the post contrast meningeal enhancement and to evaluate for the various complications, as clinically indicated.

Lumbar puncture: After getting informed consent, patient is placed in the universal flexion position. With thorough cleaning by povidone iodine and draping, lumbar puncture was performed with aseptic precaution after identifying the L3-L4 space with the help of the iliac crest. When the spinal needle enters the subarachnoid space the cerebrospinal fluid comes out and the opening pressure is measured. Then adequate sample is drawn and sent for cytological biochemical and microbiological analysis including high sensitive CRP and lactic acid, along with special investigations, as clinically indicated.

Labarotory methods

CSF hsCRP level estimation

All specimens for investigations were collected before introduction of antibiotics. Immunoturbidimetric assay using the Dimension RxL analyzer (Siemens) with calibrators and internal controls provided by Simens and according to manufacturer's recommendations was used to analyse hsCRP levels. This is a latex immunoassay developed to accurately and reproducibly measure hs CRP. The CRP present in the sample reacts with the anti- CRP antidody adsorbed into latex causing agglutination. This agglutination is identified as an absorbance change(572 nm), with the rate of change being proportional to the quantity of hs CRP in the sample.

CSF lactic acid estimation

An enzymatic method using nicotinamide adenine dinucleotide and lactic dehydrogenase (Sigma technical bulletin no. 726 UV and no. 326 UV revised,

June 1976, Sigma Chemical Co., St. Louis, Mo.) was employed for lactic acid estimation. Readings were taken with a Coleman Junior II 6/20 spectrophotometer at 340 nm. Standard curves of known lactic acid concentrations were used to determine the unknown lactic acid concentration in the specimen. Results were expressed in milligrams per deciliter.

Following statistical methods have been employed in the present study

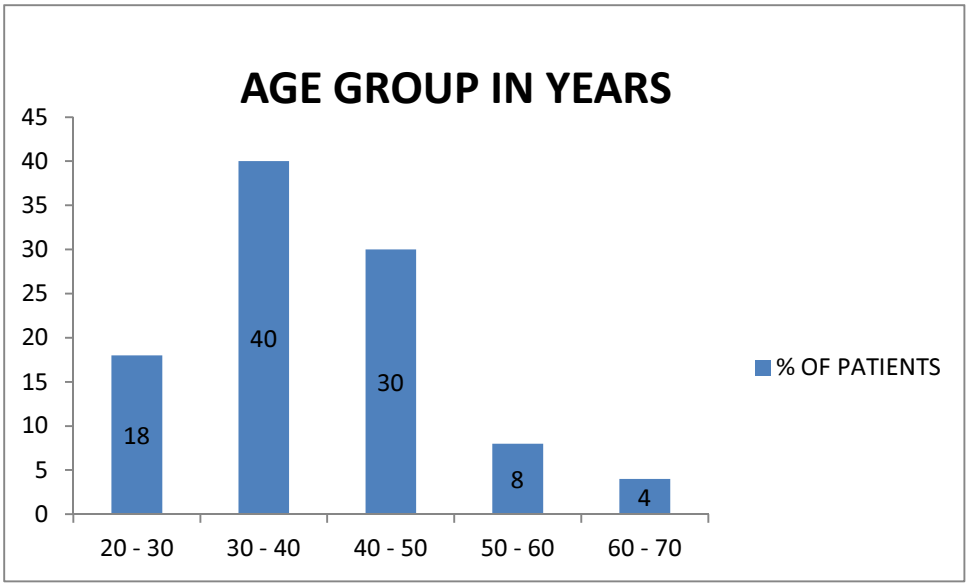
- Independent samples 't' test- Unpaired
- One way analysis of variance (ANOVA)
- Fischer's exact test.

The study was approved by the ethics committee of the institution.

RESULTS

Table 1: Age Incidence

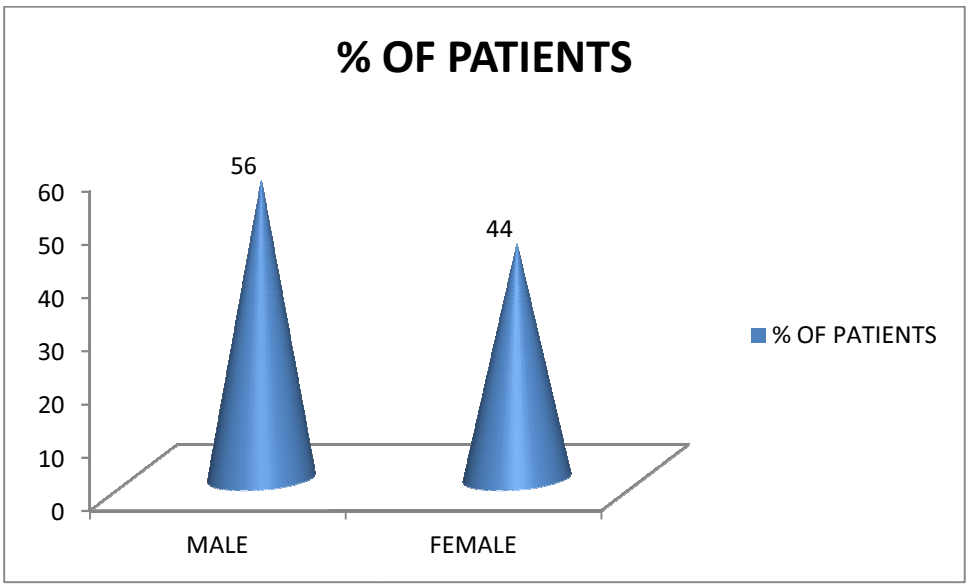
AGE	NO. OF PATIENTS	%
20 - 30	9	18
30 - 40	20	40
40 - 50	15	30
50 - 60	4	8
60 - 70	2	4



In the study group of 50 patients with meningitis, 40% were in the age group of 30-40, 30% in the age group of 40-50, 18% in the age group of 20-30, 8% in the age group of 50-60 years and 4% in the age group of 60 - 70 years. The maximum incidence of meningitis was seen in the age group of 30 – 40 years.

Table 2: Sex Incidence

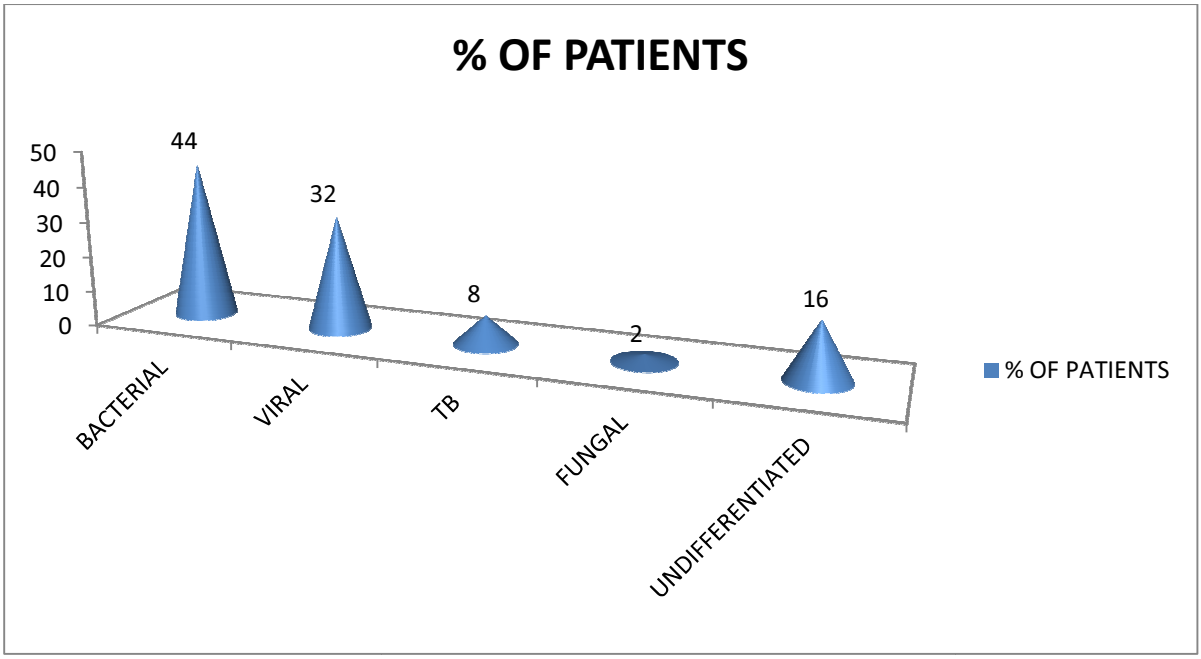
SEX	NO. 0F PATIENTS	%
MALE	28	56
FEMALE	22	44



In the study group of 50 patients with meningitis, 56% were males and 44% were females. In both the sex, maximum incidence was seen in the age group of 30 – 40 years.

Table 3: Various types of meningitis differentiated by conventional methods and CSF PCR

TYPE OF MENINGITIS	BACTERIAL	VIRAL	TB	FUNGAL	UNDIFFERENTIATED
NO.OF PATIENTS	22	16	3	1	8
% OF PATIENTS	44	32	6	2	16



Among 50 patients with meningitis, conventional methods like CSF sugar, protein, cell count, cytology, gram staining, AFB staining, culture & sensitivity and Blood culture were used and CSF PCR was used for some patients and 44% were found to have bacterial meningitis, 32% viral, 6% tuberculous, 2% fungal and 16% remained undifferentiated.

Table 4: Showing the various conventional parameters and their mean values used for the differentiation of pyogenic and viral meningitis/encephalitis

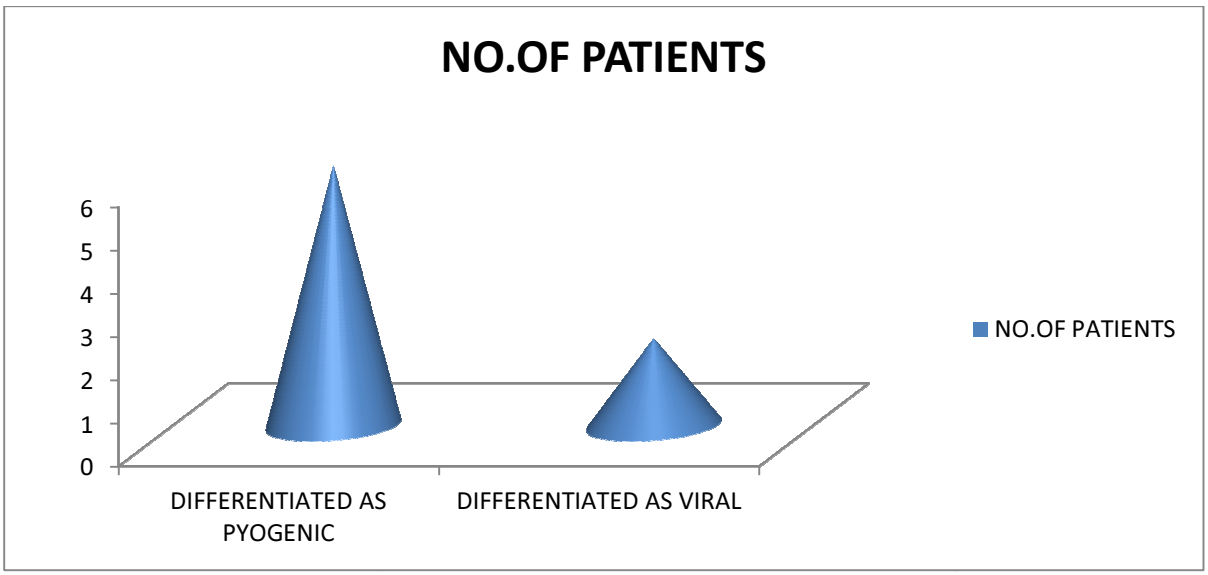
Parameter	Pyogenic=22	Viral=16	P value
Age in years	Mean=41.8,S.D=10.2	35.5,8.43	0.1123(NS)
Sex	M=10,F=12	M=10,F=6	>0.05(NS)
Mean CSF/serum glu.ratio	0.3318	0.575	<0.0001(S)
Mean CSF protein in mg/dl	368.72	84.68	0.0005(S)
Mean CSF cell count cells/µl	1270	173	0.0668(not quite sig.)

Among the 50 patients included in our study, 22 were found to have pyogenic meningitis. The mean age in years was 41. Out of the 22 patients, 10 were males and 12 were females. 13 patients showed CSF culture positivity and 9 patients showed blood culture positivity. The mean CSF/serum glucose ratio was 0.3318 and mean CSF protein was 368.72 mg/dl and the mean CSF cell count was 1270 cells/ µl. 16 were found to have viral meningitis/encephalitis. 12 patients were found positive for CSF HSV1 PCR and 4 positive for Enterovirus PCR testing in CSF. The mean age in years was 35.5. 10 were males and 6 were females. The mean CSF/serum glucose ratio was 0.575 and mean CSF protein was 84.68 mg/dl and the mean CSF cell count was 173 cells/ µl.

There was no significant difference in age and incidence among the two groups (P value >0.05). There was a significant difference in CSF protein level and CSF/serum glucose ratio between the two groups (P<0.05). The difference in cell count between the two groups was not quite significant.

Table 5: Showing the number of meningitis undifferentiated by conventional methods but differentiated by CSF hsCRP and Lactate

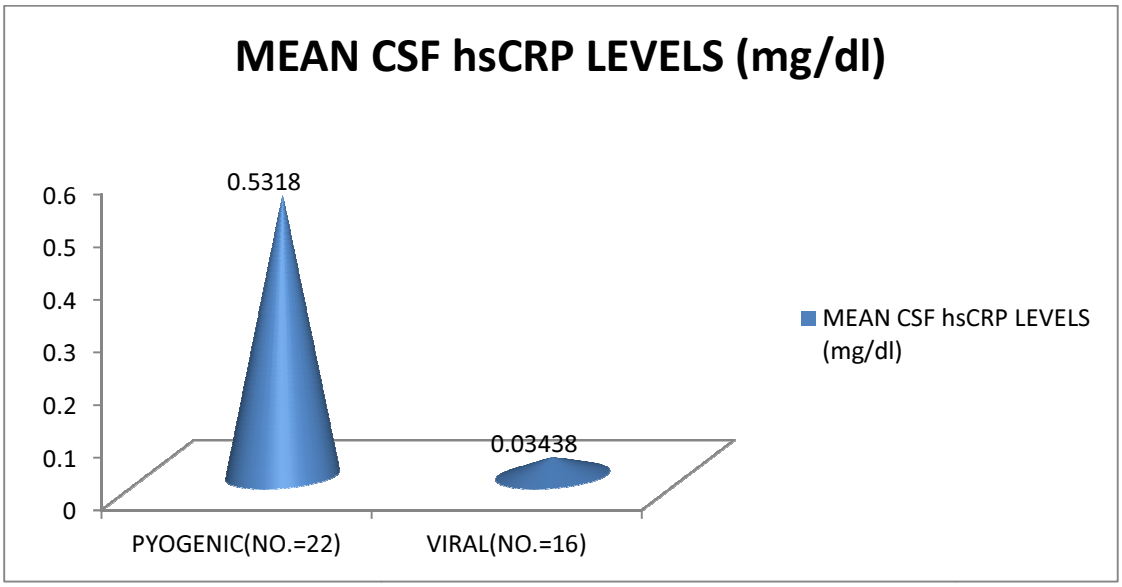
TYPES	NO.OF PATIENTS
DIFFERENTIATED AS PYOGENIC	6
DIFFERENTIATED AS VIRAL	2



Out of the 8 patients with meningitis undifferentiated by conventional methods, 6 patients were differentiated as probable patients with pyogenic meningitis and 2 as viral based on CSF hsCRP and Lactate levels.

Table 6: Showing mean CSF hsCRP levels in bacterial and viral meningitis/encephalitis differentiated by conventional methods

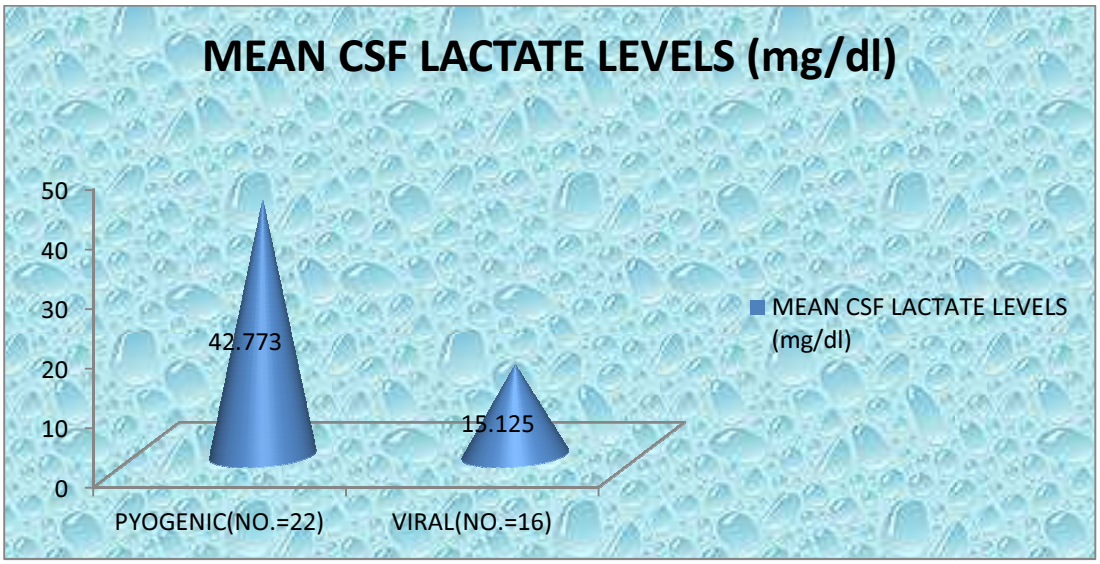
TYPE OF MENINGITIS	MEAN CSF hsCRP LEVELS
PYOGENIC(NO.=22)	0.5318(mg/dl)
VIRAL(NO.=16)	0.03438(mg/dl)



The mean CSF hsCRP levels in bacterial and viral meningitis/encephalitis differentiated by conventional methods was 0.5318 and 0.03438 mg/dl respectively. The reference normal range is between 0.01- 0.05 mg/dl. The significance was analysed using the unpaired t test and the P value was < 0.0001, extremely significant.

Table 7: Showing mean CSF Lactate levels in bacterial and viral meningitis/encephalitis differentiated by conventional methods

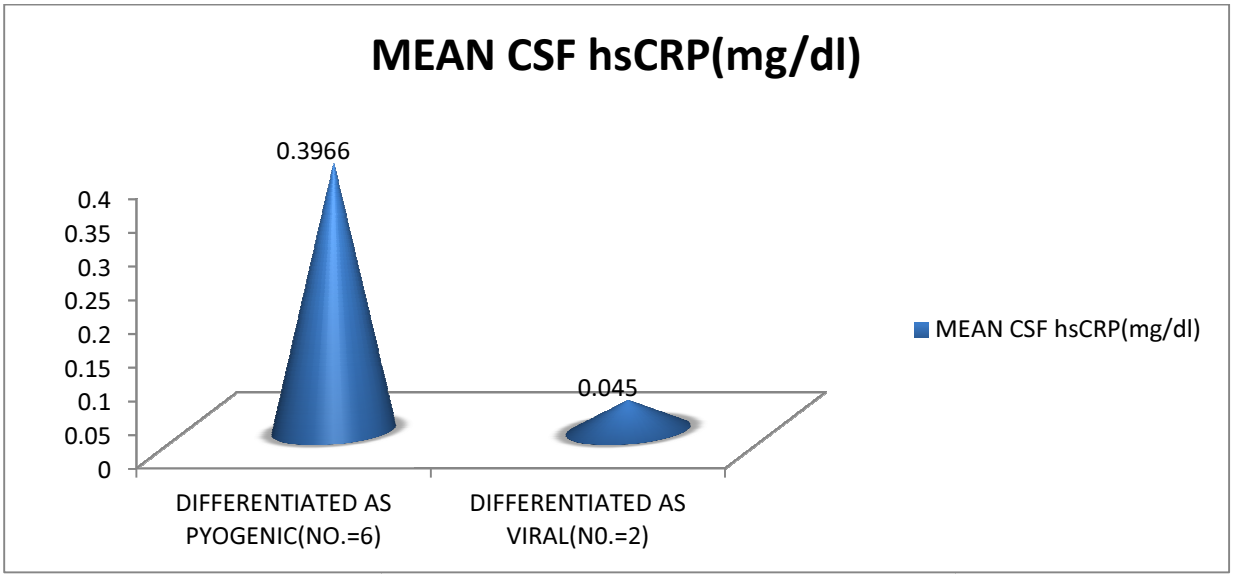
TYPE OF MENINGITIS	MEAN CSF LACTATE LEVELS (mg/dl)
PYOGENIC(NO.=22)	42.773
VIRAL(NO.=16)	15.125



The mean CSF Lactate levels in bacterial and viral meningitis/encephalitis differentiated by conventional methods was 42.773 and 15.125 mg/dl respectively. The reference normal range is between 10 – 20 mg/dl. The significance was analysed using the unpaired t test and the P value was < 0.0001, extremely significant.

Table 8: Showing mean CSF hsCRP levels in bacterial and viral meningitis/encephalitis undifferentiated by conventional methods but differentiated by CSF hsCRP

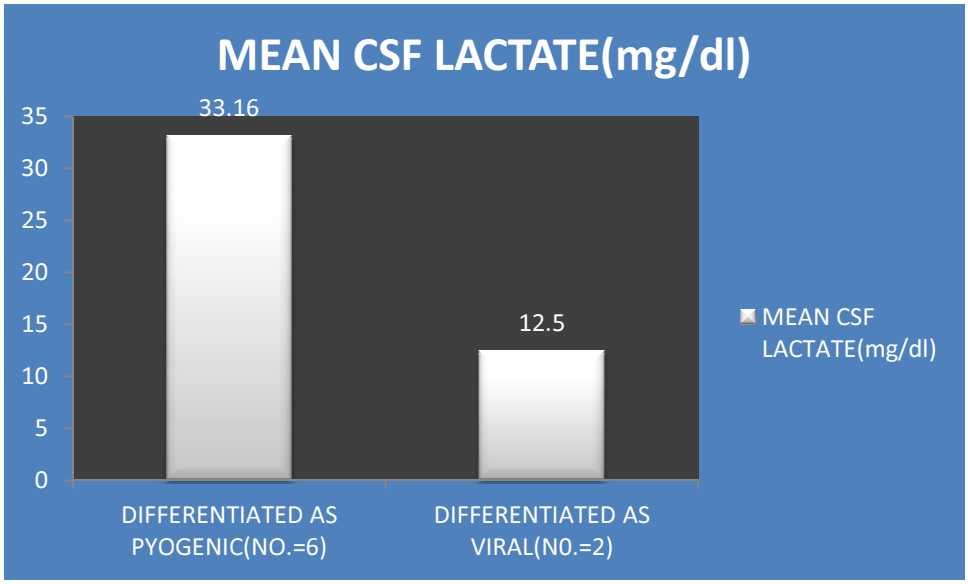
TYPES	MEAN CSF hsCRP(mg/dl)
DIFFERENTIATED AS PYOGENIC(NO.=6)	0.3966
DIFFERENTIATED AS VIRAL(N0.=2)	0.045



The mean CSF hsCRP levels in bacterial and viral meningitis/encephalitis undifferentiated by conventional methods but differentiated by CSF hsCRP was 0.3966 and 0.045 mg/dl respectively. The reference normal range is between 0.01- 0.05 mg/dl.

Table 9: Showing mean CSF Lactate levels in bacterial and viral meningitis/ encephalitis undifferentiated by conventional methods but differentiated by CSF Lactate

TYPES	MEAN CSF LACTATE(mg/dl)
DIFFERENTIATED AS PYOGENIC(NO.=6)	33.16
DIFFERENTIATED AS VIRAL(N0.=2)	12.5



The mean CSF Lactate levels in bacterial and viral meningitis/encephalitis undifferentiated by conventional methods but differentiated by CSF Lactate was 33.16 and 12.5mg/dl respectively. The reference normal range is between 10 – 20 mg/dl.

Table 10: Showing sensitivity and specificity of CSF hsCRP in the differentiation of pyogenic and non pyogenic meningitis

hsCRP	TYPE OF MENINGITIS	
	PYOGENIC	NON PYOGENIC
INCREASED	21(a)	1(b)
NORMAL	1©	19(d)

Sensitivity = (a/a+c) × 100 = 21/22 × 100 = 95.45 %

Specificity = (d/b+d) × 100 = 19/20 × 100 = 95%

Predictive value of a positive test = (a/a+b) × 100 = 21/22 × 100 = 95.45%

Predictive value of a negative test = (d/c+d) × 100 = 19/20 × 100 = 95%

Percentage of false negatives = (c/a+c) × 100 = 1/22 × 100 = 4.54%

Percentage of false positives = (b/b+d) × 100 = 1/20 × 100 = 5%

Sensitivity and Specificity of CSF hsCRP for differentiating Pyogenic from non-pyogenic meningitis was 95.45% and 95% respectively. The Predictive value of a positive test was 95.45% and the predictive value of a negative test was 95%. The Percentage of false negatives was 4.54% and the percentage of false positives was 5%. The likelihood ratio was 19.091. The one false positive case had fungal meningitis. The two-sided P value using the Fischer's exact test was < 0.0001, considered extremely significant.

Relative risk = 19.091

95% Confidence Interval: 2.819 to 129.31

(using the approximation of Katz.)

Table 11: Showing sensitivity and specificity of CSF Lactate in the differentiation of pyogenic and non pyogenic meningitis

LACTATE	TYPE OF MENINGITIS	
	PYOGENIC	NON PYOGENIC
INCREASED	20(a)	4(b)
NORMAL	2©	16(d)

Sensitivity = (a/a+c) × 100 = 20/22 × 100 = 90.9 %

Specificity = (d/b+d) × 100 = 16/20 × 100 = 80%

Predictive value of a positive test = (a/a+b) × 100 = 20/24 × 100 = 83.33%

Predictive value of a negative test = (d/c+d) × 100 = 16/18 × 100 = 88.88%

Percentage of false negatives = (c/a+c) × 100 = 2/22 × 100 = 9.09%

Percentage of false positives = (b/b+d) × 100 = 4/20 × 100 = 20%

Sensitivity and Specificity of CSF Lactate for differentiating Pyogenic from non-pyogenic meningitis was 90.9% and 80% respectively. The Predictive value of a positive test was 83.33% and the predictive value of a negative test was 88.88%. The Percentage of false negatives was 9.09% and the percentage of false positives was 20%. The likelihood ratio was 4.545. Out of the 4 false positive cases 3 were found to have TB meningitis and 1 had fungal meningitis. The two-sided P value using the Fischer's exact tect was < 0.0001, considered extremely significant.

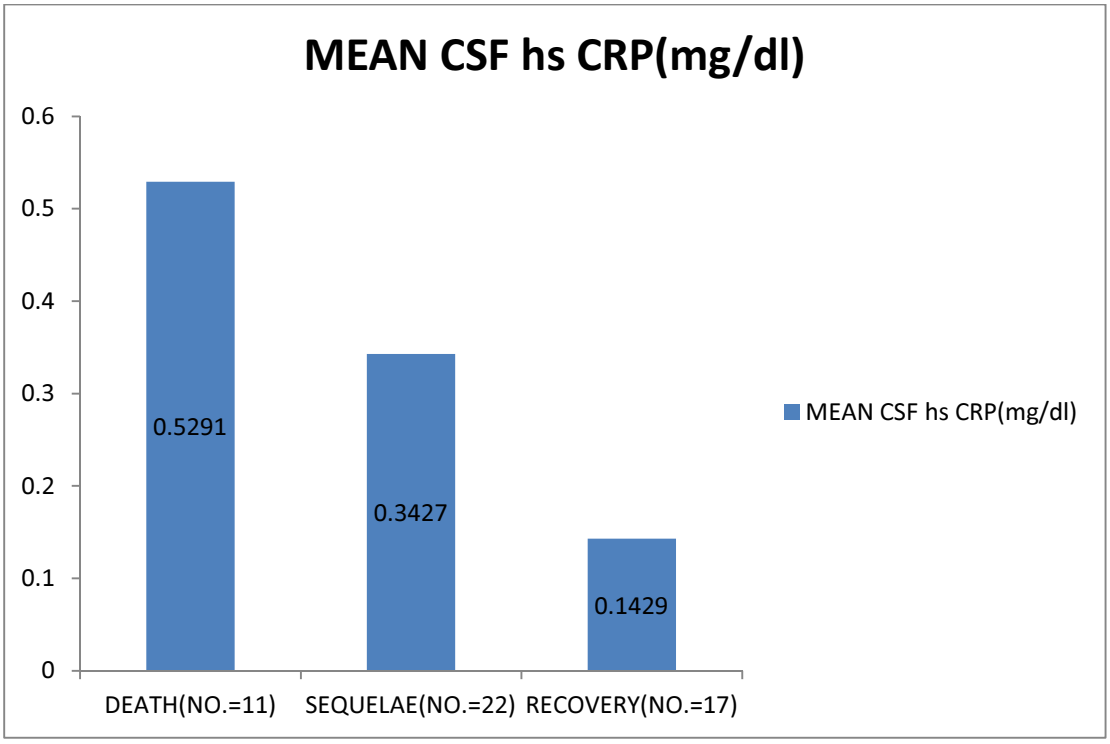
Relative risk = 7.500

95% Confidence Interval: 2.005 to 28.052

(using the approximation of Katz.)

Table 12: Showing mean CSF hsCRP levels in various outcomes of meningitis

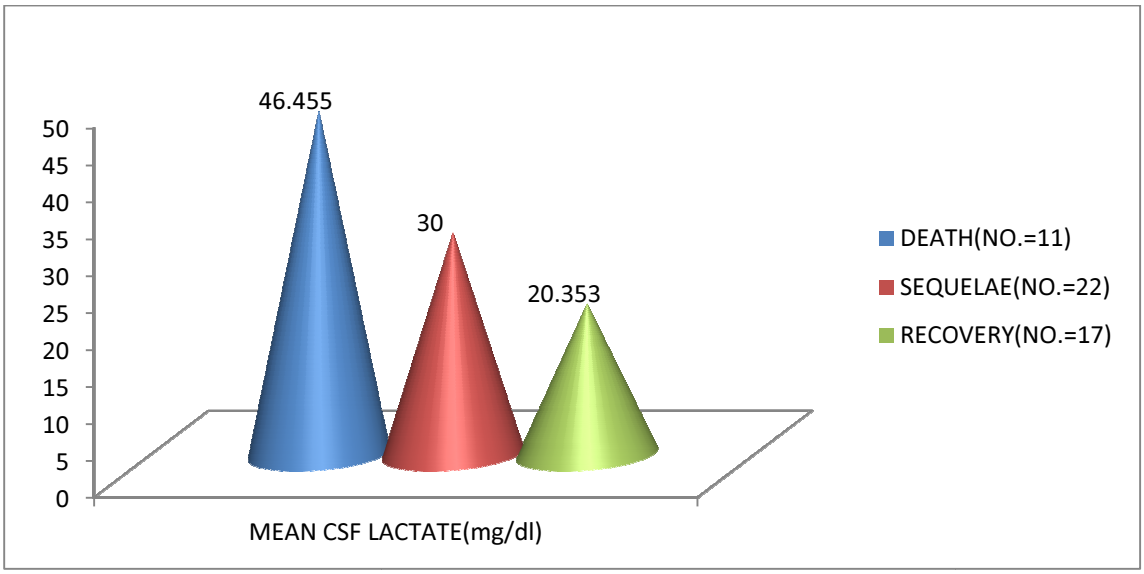
OUTCOME	DEATH(NO.=11)	SEQUELAE(NO.=22)	RECOVERY(NO.=17)
MEAN CSF hs CRP(mg/dl)	0.5291	0.3427	0.1429



The mean CSF levels of hsCRP among patients who expired was 0.5291, patients who survived with sequelae was 0.3427, patients who recovered completely was 0.1429 mg/dl. The mean CSF levels of hsCRP in various outcomes of meningitis was compared using Analysis Of Variance (ANOVA) and it was found significant with P value < 0.0001.

Table 13: Showing mean CSF Lactate levels in various outcomes of meningitis

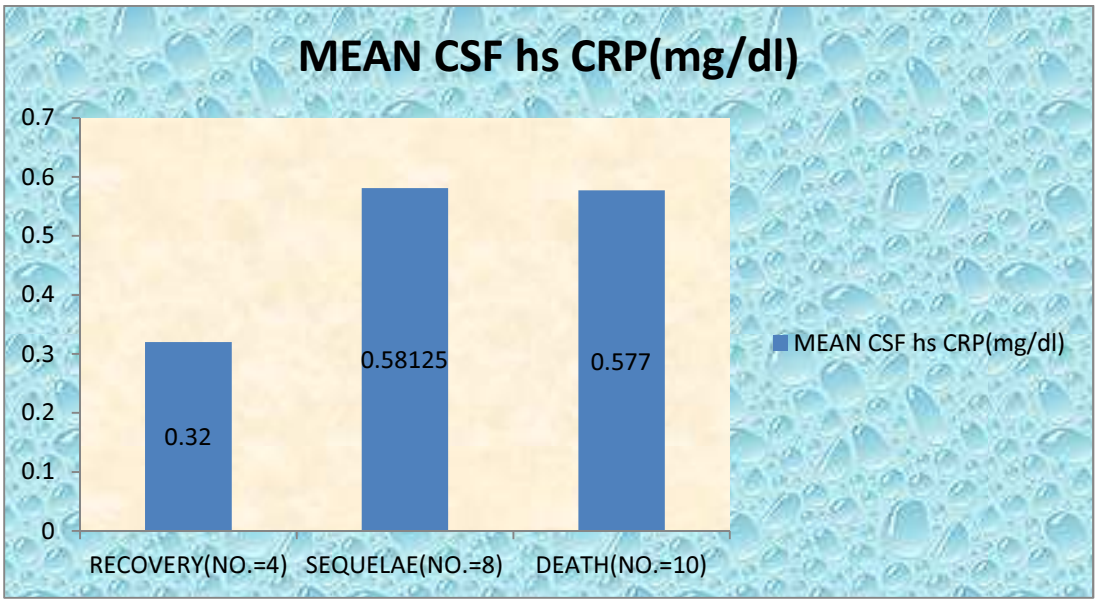
OUTCOME	DEATH(NO.=11)	SEQUELAE(NO.=22)	RECOVERY(NO.=17)
MEAN CSF LACTATE(mg/dl)	46.455	30	20.353



The mean CSF levels of Lactate among patients who expired was 46.455, patients who survived with sequelae was 30, patients who recovered completely was 20.353 mg/dl. The mean CSF levels of Lactate in various outcomes of meningitis was compared using Analysis Of Variance (ANOVA) and it was found significant with P value < 0.0001.

Table 14: Showing mean CSF hsCRP levels in various outcomes of pyogenic meningitis

OUTCOME	RECOVERY(NO.=4)	SEQUELAE(NO.=8)	DEATH(NO.=10)
MEAN CSF hs CRP(mg/dl)	0.32	0.58125	0.577



Among the 22 patients of pyogenic meningitis differentiated by conventional methods,the mean CSF hsCRP values of patients who recovered completely, who survived with sequelae, who expired were 0.32, 0.58125, 0.577 mg/dl respectively. The significance of means was analysed using the ANOVA and the P value was 0.0373, considered significant.

Variation among column means is significantly greater than expected by chance.

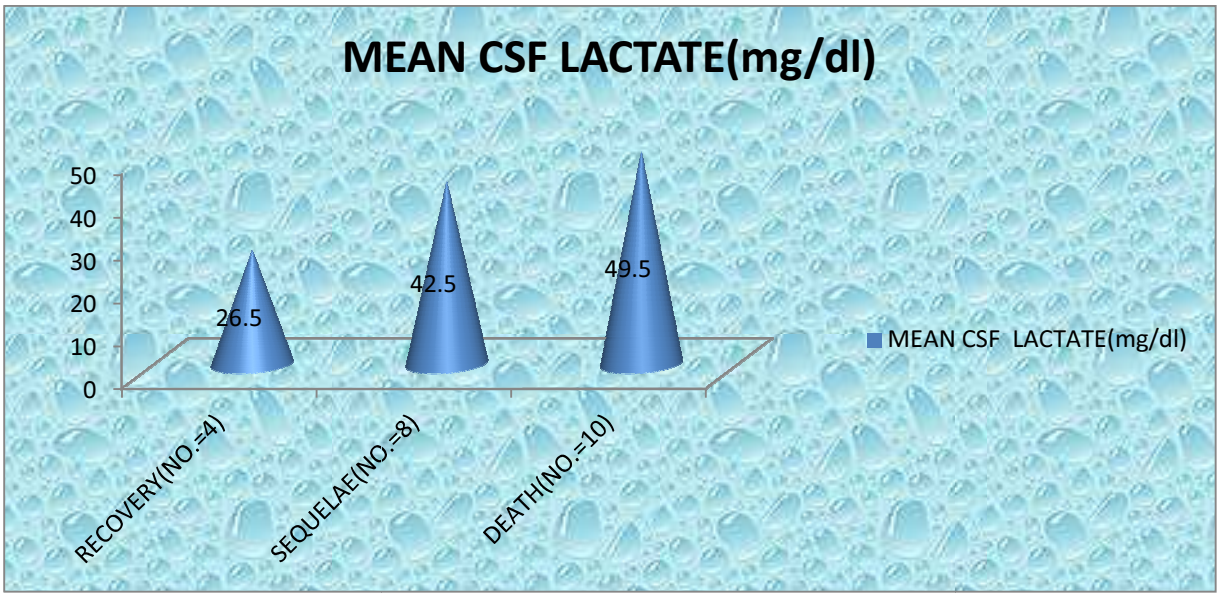
According to the Tukey-Kramer Multiple Comparisons test, if the value of q is greater than 3.593 then the P value is less than 0.05.

Comparison	Mean Difference	q		P value
Column A vs Column B	-0.2613	3.611	*	P<0.05
Column A vs Column C	-0.2570	3.677	*	P<0.05
Column B vs Column C	0.004250	0.07585	ns	P>0.05

Although the difference in CSF hsCRP values between patients who survived with sequelae and patients who expired was not significant, the difference in CSF hsCRP values between patients who recovered completely and patients who survived with sequelae, expired was significant as shown above.

Table 15: Showing mean CSF Lactate levels in various outcomes of pyogenic meningitis

OUTCOME	RECOVERY(NO.=4)	SEQUELAE(NO.=8)	DEATH(NO.=10)
MEAN CSF LACTATE(mg/dl)	26.5	42.5	49.5



Among the 22 patients of pyogenic meningitis differentiated by conventional methods,the mean CSF Lactate values of patients who recovered completely, who survived with sequelae, who expired were 26.5, 42.5, 49.5 mg/dl respectively. The significance of means was analysed using the ANOVA and the P value was 0.0010, considered extremely significant.

DISCUSSION

We analysed 50 patients admitted with various symptoms and signs of meningitis like fever, headache, altered sensorium, seizures, neck stiffness. These patients were admitted in our Rajiv Gandhi Government General Hospital during the months of June 2012 to November 2012.

Patients with contraindications for lumbar puncture like those with coagulopathy, documented Intracranial space occupying mass lesion and local infection at sites of lumbar puncture, and patients with pyogenic infections elsewhere with tissue necrosis and those with malignancy, those with severe hepatic failure and dyslipidemia, patients on long term steroids and OCP, patients with recent history of stroke were excluded from the study as these would cause elevation of the biomarkers.

Patients with altered sensorium were subjected to CT Brain before doing LP. Other patients were subjected to LP after sending blood culture samples. CSF analysis for glucose, CSF/serum glucose ratio, protein, cell count, cytology, gram staining, AFB staining, bacterial and blood culture were used.CSF India ink staining was used in 1 patient. CSF PCR was used in some patients. CSF hsCRP and Lactate assay were done in all patients.

In the study group of 50 patients with meningitis, 40% were in the age group of 30-40, 30% in the age group of 40-50, 18% in the age group of 20-30, 8% in the age group of 50-60 years and 4% in the age group of 60 - 70 years. The maximum incidence of meningitis was seen in the age group of 30 – 40 years. 56% were males and 44% were females.

Out of the 50 patients, 44% were found to have bacterial meningitis, 32% viral, 6% tuberculous, 2% fungal and 16% remained undifferentiated.

22 patients were proved to be pyogenic through the conventional methods. 13 patients had CSF culture positivity for bacteria. Out of the 13 patients, 5 patients had both gram staining and CSF culture positivity. The remaining 8 patients had only culture positivity. The organisms identified by culture were Pneumococci in 8 patients, H.influenzae and Group B Streptococccci in 2 patients each and Meningococci in 1 patient. 9 patients had blood cuture positivity. The organisms grown in blood culture were Pneumococci in 4 patients, Meningococci in 1 patient and Group B Streptococci in 4 patients.

16 patients were differentiated as having viral meningitis/encephalitis. Patients were diagnosed to have viral etiology based on the typical CSF findings of normal glucose, slightly elevated protein and lymphocytic pleocytosis and the negative gram stain, the absence of bacterial growth in blood and CSF cultures.

CSF PCR for HSV 1 was found positive in 12 patients and enteroviral CSF PCR in 4 patients.

Out of the 3 patients found to have TB meningitis, 2 patients had history of prolonged fever with chest X ray showing military mottling and MRI brain showing basal exudates. The third patient had history of pulmonary tuberculosis on ATT intensive phase and his MRI brain also showed exudates.

1 patient was diagnosed as a case of fungal meningitis. He was positive for HIV ELISA testing and hence CSF was sent for India ink staining and found positive. 8 patients could not be differentiated as to the type of meningitis.

Among patients with pyogenic patients, the mean age in years was 41. Out of the 22 patients, 10 were males and 12 were females. The mean CSF/serum glucose ratio was 0.3318 and mean CSF protein was 368.72 mg/dl and the mean CSF cell count was 1270 cells/ µl. 16 were found to have viral meningitis/encephalitis. The mean age in years was 35.5. Out of the 16 patients, 10 were males and 6 were females. The mean CSF/serum glucose ratio was 0.575 and mean CSF protein was 84.68 mg/dl and the mean CSF cell count was 173 cells/ µl.

There was no significant difference in age and incidence among the two groups, patients with pyogenic and viral meningitis/encephalitis (P value

>0.05). There was a significant difference in CSF protein level and CSF/serum glucose ratio between the two groups (P<0.05). The difference in cell count between the two groups was not significant.

The mean CSF hsCRP and Lactate values among patients differentiated as pyogenic and viral were 0.5318, 0.03438 mg/dl and 42.773, 15.125 mg/dl respectively. The significance of difference between these two values was analysed using the unpaired t test and it was found to be extremely significant with a P value < 0.0001. Hence we could infer that CSF hsCRP and CSF Lactate differed markedly in patients with pyogenic and viral meningitis/encephalitis and both are useful markers for early identification of pyogenic meningitis and its prompt treatment. This result is similar to the results of studies on the significance of CSF hsCRP for differentiating pyogenic and non – pyogenic meningitis conducted by Vaishnavi et al[69], Przylalkowski et al[68], Anil kumar et al[67], Tankhiwale et al[70]. Studies conducted by Ali Hassan Abro et al[65], Smith et al[71], Genton et al[72], Klien et al[53] showed similar results using CSF Lactate.

Out of the 8 patients undifferentiated by conventional methods, 6 patients had elevated CSF hsCRP, the mean value being 0.3966 mg/dl compared to the reference value of 0.01 – 0.05 mg/dl. Their mean CSF Lactate value was 33.16 mg/dl compared to the reference value of 10 – 20 mg/dl. These 6 patients were treated as pyogenic meningitis based on CSF hsCRP and Lactate and they

responded to treatment. 2 patients undifferentiated by the conventional method had normal hsCRP (mean = 0.045 mg/dl) and CSF Lactate (mean=12.5 mg/dl) and they were treated as viral meningitis/encephalitis and they also responded to treatment. Hence we inferred that CSF hsCRP and Lactate are also useful in differentiating cases which are undifferentiated by the conventional methods.

Out of the 22 patients differentiated as pyogenic by conventional methods, 21 patients had elevated CSF hsCRP levels and 1 patient had normal values. Out of the 20 patients differentiated to be non-pyogenic(16 viral, 3 TB, 1 fungal) 19 patients had normal CSF hsCRP values and the patient with fungal meningitis had increased CSF hsCRP. The CSF hsCRP of that patient was 0.06 mg/dl with the normal reference range being 0.01 – 0.05 mg/dl. Hence the Sensitivity CSF hsCRP for differentiating Pyogenic from non- pyogenic meningitis was 95.45% with 95% Confidence Interval of 0.7717 to 0.99880 and the Specificity was 95% with 95% Confidence Interval of 0.7513 to 0.99870. The Predictive value of a positive test was 95.45% and the predictive value of a negative test was 95%. The Percentage of false negatives was 4.54% and the percentage of false positives was 5%. The likelihood ratio was 19.091. The two-sided P value using the Fischer's exact test was < 0.0001, considered extremely significant. This is

in par with the EFNS guideline on the management of community-acquired bacterial meningitis published in the European Journal of Neurology 2008[66].

Out of the 22 patients differentiated as pyogenic by conventional methods, 20 patients had elevated CSF Lactate levels and 2 patients had normal values. Out of the 20 patients differentiated to be non-pyogenic(16 viral, 3 TB, 1 fungal) 16 patients had normal CSF Lactate values and the patients with fungal and TB meningitis had increased CSF Lactate. Hence the Sensitivity of CSF Lactate for differentiating Pyogenic from non- pyogenic meningitis was 90.9% with 95% Confidence Interval of 0.7083 to 0.9888 and the Specificity was 80% with 95% Confidence Interval of 0.5633 to 0.9427 . The Predictive value of a positive test was 83.33% and the predictive value of a negative test was 88.88% respectively. The Percentage of false negatives was 9.09% and the percentage of false positives was 20%. The likelihood ratio was 4.545. The two-sided P value using the Fischer's exact test was < 0.0001, considered extremely significant. This is in par with the EFNS guideline on the management of community-acquired bacterial meningitis published in the European Journal of Neurology 2008[66].

Among the 22 patients of pyogenic meningitis differentiated by conventional methods, the mean CSF hsCRP values of patients who recovered completely, who survived with sequelae, who expired were 0.32, 0.58125, 0.577 mg/dl respectively. The significance of means was analysed using the ANOVA and the P value was 0.0373, considered significant. Though the mean CSF hsCRP levels in patients who survived with sequelae and those who expired did not differ much, there was a significant difference in mean hsCRP levels among patients who recovered completely and the other two categories. Hence it is concluded that CSF hsCRP can also be used as a marker of prognostication in pyogenic meningitis. Similar results were found out by S Nouira et al[73] in their study.

Again among the 22 patients of pyogenic meningitis differentiated by conventional methods, the mean CSF Lactate values of patients who recovered completely, who survived with sequelae, who expired were 26.5, 42.5, 49.5 mg/dl respectively. The significance of means was analysed using the ANOVA and the P value was 0.0010, considered extremely significant. Hence it is concluded that CSF Lactate can also be used as a marker of prognostication in pyogenic meningitis. Similar results have been produced by Ali Hassan Abro[65] et al in their study.

In summary though the CSF biomarkers like hsCRP and Lactate are not used routinely to aid in the differential diagnosis of meningitis, several studies have

shown that these biomarkers are valuable in the differential diagnosis. Our study has also shown that CSF hsCRP and Lactate are not only useful in the differential diagnosis but also as prognostication markers.

Our study had certain limitations. The sample size of our study was less. We could not use controls to show the normal CSF reference values of lactate and hsCRP as doing LP and drawing CSF from healthy people is not acceptable.

CONCLUSION

- The Cerebrospinal fluid level of hs-CRP is elevated in acute pyogenic meningitis and hence it is useful to differentiate it from viral meningitis/encephalitis.

- The Cerebrospinal fluid level of Lactic acid is elevated in acute pyogenic meningitis besides fungal and tuberculous meningitis and hence it is useful to differentiate it from viral meningitis/encephalitis.

- Therefore the hs-CRP and Lactic acid assays in Cerebrospinal fluid is highly useful in the management aspects whenever the diagnosis is uncertain by conventional methods.

- The Cerebrospinal fluid level of hsCRP is significantly elevated in patients who expired and in patients with post meningitic sequelae than in patients recovered uneventfully. So it may be used as a marker of prognostication in acute pyogenic meningitis.

- The Cerebrospinal fluid level of Lactate is significantly elevated in patients who expired than in patients with post meningitis sequelae and is even lower in patients who recovered uneventfully. Hence it predicts the clinical outcome better and it can be used as a marker of prognostication in acute pyogenic meningitis.

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ROLE OF CEREBROSPINAL FLUID LEVELS OF C-REACTIVE PROTEIN AND LACTATE IN ACUTE MENINGITIS

NAME:

AGE:

SEX:

ADDRESS:

OCCUPATION:

DURATION AND DETAILS OF ILLNESS:

SYMPTOMS:

- Fever
- Vomiting
- Headache
- Neck stiffness
- Seizures-Focal/GTCS
- Depressed level of Consciousness
- Focal Deficits-Blindness,Double Vision,Bulbar Symptoms,Hemiparesis.

PAST HISTORY:

- Diabetes
- Hypertension
- Tuberculosis

DRUG HISTORY:

PERSONAL HISTORY:

- Smoking
- Alcoholism

GENERAL EXAMINATION:

Hydration Status

PULSE: **BLOOD PRESSURE:**

GENERAL EXAMINATION:

SYSTEMIC EXAMINATION:

CVS: RS: ABDOMEN: CNS:

INVESTIGATIONS:

Hb: TC: DC: P- L- E- M- Plt: ESR:

Blood Glucose Random :

Blood Urea :

Serum Creatinine :

Serum Electrolytes : Na+ K+

LIVER FUNCTION TEST :

Bilirubin Total :
Direct :

SGOT :

SGPT :

Total Protein :
Albumin :
Globulin :

Sr. Alkaline Phosphatase :

COAGULATION PROFILE:

URINE EXAMINATION:

Sugar : Deposits:

Albumin :

ECG:

X-RAY CHEST PA VIEW :

CT BRAIN-PLAIN &
(CONTRAST,IF NEEDED) :

MRI BRAIN-PLAIN &
CONTRAST(IF NEEDED) :

BLOOD CULTURE &
SENSITIVITY :

TREATMENT GIVEN :

LUMBAR PUNCTURE FOR CEREBRO SPINAL FLUID ANALYSIS:
Biochemistry:Protein,Sugar
Cell counting,Cytological evaluation.
Microbioology:Gram&AFB Staining,Culture&Sensitivity.
High sensitive C-reactive protein level.
Lactate level.

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No: 04425305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. Sakthivel .R
PG in MD General Medicine
Madras Medical College, Chennai -3

Dear Dr. Sakthivel .R

The Institutional Ethics Committee of Madras Medical College reviewed and discussed your application for approval of the proposal entitled "Role of cerebrospinal fluid levels of highly sensitive c- reactive protein and lactate in acute meningits" No. 24052012.

The following members of Ethics Committee were present in the meeting held on 30.05.2012 conducted at Madras Medical College, Chennai -3.

1.	Prof. S.K. Rajan, MD	-- Chairperson
2.	Prof. Pregna B. Dolia MD Vice Principal , Madras Medical College, Chennai -3 Director , Instt.of Bio Chemistry, MMC, Ch-3	-- Member Secretary
3.	Prof R. Nandhini, MD Director, Institute of Pharmacology, MMC, Ch-3	-- Member
4.	Prof. P. Karkuzhali MD Director i/c Prof & Head , Dept. of Pathology, MMC, Ch-3	-- Member
5.	Prof.A. Radhakrishnan MD Prof. of Internal Medicine, MMC, Ch-3	-- Member
6.	Prof. P. Raghumani MS Prof. of Surgery, Dept. of Surgery, MMC, Chennai -3	-- Member
7.	Thiru. S. Govindasamy . BA.BL	-- Lawyer
8.	Tmt. Arnold Soulina MA	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd /. Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report

Member Secretary, Ethics Committee

Serial no.	Age,Sex	Symptoms and signs on admission					H/O prior treat.		
		Fever	Headache	Altered sensorium	Seizures	Neck stiffness		CSF/Serum glucose (N <0.4)	Glucose 40-70 mg/dl
1	39,M	P	P	P	A	P	A	0.3	20
2	22,F	P	P	p	A	P	A	0.2	22
3	26,M	P	P	A	A	A	A	0.6	55
4	36,M	A	P	P	A	P	P	0.6	58
5	39,F	P	P	A	A	A	A	0.6	55
6	40,F	P	P	P	P	P	A	0.4	40
7	44,F	P	P	P	A	P	P	0.5	55
8	63,M	P	P	A	A	P	P	0.3	28
9	35,F	P	P	P	P	P	A	0.4	45
10	35,F	P	P	p	P	P	P	0.6	46
11	38,F	P	P	P	A	P	A	0.2	26
12	43,M	P	P	P	A	P	A	0.7	65
13	49,F	P	P	P	P	P	A	0.6	30
14	47,F	P	P	A	A	P	A	0.45	42
15	41,M	P	P	A	A	P	A	0.5	45
16	25,M	P	P	A	A	P	P	0.5	45
17	29,M	P	P	A	A	P	A	0.5	45
18	30,M	P	P	A	A	P	P	0.3	30
19	60,M	P	P	A	A	P	P	0.2	22
20	55,M	P	P	A	A	P	A	0.7	67
21	58,F	P	P	P	A	P	A	0.3	25
22	50,M	P	P	A	A	P	A	0.5	45
23	48,M	P	P	A	A	P	A	0.6	75
24	46,F	P	P	A	A	P	A	0.25	28
25	40,M	P	P	A	A	P	P	0.5	56
26	42,F	P	P	A	A	P	A	0.3	28
27	45,F	P	P	P	A	P	P	0.1	55
28	31,M	P	P	A	A	P	P	0.4	40
29	28,F	P	P	P	A	P	A	0.7	75
30	27,M	P	P	A	A	P	A	0.6	70
31	32,M	P	P	A	A	P	A	0.25	28

32	34,F	P	P	P	A	P	A	0.5	55
33	40,M	P	P	P	A	P	P	0.5	65
34	42,F	P	P	P	A	P	P	0.1	28
35	28,F	P	P	P	A	P	P	0.5	64
36	35,M	P	P	P	A	P	A	0.4	38
37	39,M	P	P	P	A	P	A	0.45	55
38	37,M	P	P	P	A	P	A	0.6	70
39	26,M	P	P	P	A	P	A	0.55	60
40	29,M	P	P	P	A	P	A	0.55	55
41	31,M	P	P	P	A	P	A	0.3	24
42	35,F	P	P	A	A	P	P	0.6	65
43	42,F	P	P	P	A	P	A	0.7	75
44	32,M	P	P	P	A	P	A	0.5	45
45	30,F	P	P	P	A	P	A	0.6	60
46	36,M	P	P	P	P	P	A	0.15	25
47	41,F	P	P	P	A	P	P	0.35	35
48	42,F	P	P	P	A	P	A	0.3	30
49	40,M	P	P	p	A	P	P	0.55	75
50	50,M	P	P	A	A	P	P	0.45	55

keywords: CSF-cerebrospinal fluid, A-Absent, P-Present, L-Lymphocytes,M-Monocytes,R-RBCs, Poly-Polymorphs,Neut.-Neutrophils
UD-undifferentiated,UD treated as py-undifferentiated treated as pyogenic,UD treated as vi-undifferentiated treated as viral, TB-Tuberculous

CSF Analysis

Protein	Cell count	Cytology	C&S	Gr.stain	AFB	hsCRP	Lactate	pressure
15-50 mg/dl	**0-5 cells/µl**	**L=60-70%,M=30-50%**				0.01-0.05mg/dl	10-20 mg/dl	
570	250	Neut. 85%,L 15%	Pneumococcus	GPC in pairs	None	0.27	33	↑
68	302	Neut. 90%,L 10%	Pneumococcus	GPC in pairs	None	0.33	35	↑
56	110	L 85%,M 15%	No growth	None	None	0.01	11	N
36	25	L60%,N 40%	No growth	None	None	0.35	33	N
65	90	R60%,L 40%	No growth	None	None	0.05	16	N
390	220	Neut. 85%,L15%	No growth	None	None	0.55	35	↑
58	80	L 65%,Poly 35%	No growth	None	None	0.04	18	↑
298	7790	poly 60%,L 40%	Group B strep	None	None	0.8	34	↑
110	350	L 80%,M 20%	No growth	None	None	0.02	31	↑
45	20	L 70%,M 30%	No growth	None	None	0.58	40	↑
895	350	L 30%,Poly 70%	Pneumococcus	GPC in pairs	None	0.45	43	↑
65	250	L 70%,Poly 30%	No growth	None	None	0.05	15	↑
490	985	poly 50%,L 50%	H.influenza	None	None	0.6	49	↑
30	313	Poly 80%,L 15%	No growth	None	None	0.65	43	↑
765	420	Poly75%,M 25%	No growth	None	None	0.62	56	↑
75	250	L 75%,M 25%	No growth	None	None	0.05	11	↑
65	85	L 55%,Poly 45%	No growth	None	None	0.04	17	↑
250	110	L 75%,M 25%	No growth	None	None	0.06	22	↑
20	980	poly 55%,L 45%	Group B strep	None	None	0.65	27	N
120	110	L 75%,poly 25%	No growth	None	None	0.04	18	N
153	75	poly 52%,L 48%	Pneumococcus	None	None	0.5	56	↑
575	210	Neut.80%,L 20%	No growth	None	None	0.2	15	↑
70	65	Neut.60%,L 20%	No growth	None	None	0.05	12	↑
240	875	Poly 50%,L 50%	Pneumococcus	None	None	0.05	16	N
110	250	L65%,M 45%	No growth	None	None	0.04	14	N
230	775	Poly 50%,L 50%	No growth	None	None	0.3	40	N
575	250	Neut.85%,L 15%	Pneumococcus	None	None	0.6	50	↑
500	275	L 80%,M 20%	No growth	None	None	0.03	23	↑
120	250	L 85%,M 15%	No growth	None	None	0.02	18	↑
75	55	L 60%,Neut. 40%	No growth	None	None	0.03	17	↑
110	645	L 55%,Neut. 45%	No growth	None	None	0.65	45	↑

98	225	L 55%,M 25%,poly 20%	No growth	None	None	0.03	18	↑
75	45	L 55%,Neut.45%	No growth	None	None	0.4	40	↑
105	65	Neut.55%,L 45%	H.influenza	None	None	0.55	61	↑
770	390	Neut.80%,L 15%,M 5%	No growth	None	None	0.52	30	↑
75	323	L 60%,M 40%	No growth	None	None	0.04	18	↑
60	35	L 60%,Neut.40%	No growth	None	None	0.3	26	↑
773	5510	Neut. 85%,L 15%	Pneumococcus	GPC in pairs	None	0.61	58	↑
95	110	L 60%,M 40%	No growth	None	None	0.04	16	↑
45	100	L 55%,Neut. 45%	No growth	None	None	0.5	35	↑
110	100	L 50%,Neut. 50%	No growth	None	None	0.9	55	↑
98	230	L 60%,M 40%	No growth	None	None	0.02	12	↑
90	250	L 70%,Neut. 30%	No growth	None	None	0.01	10	↑
875	7220	Neut.85%,L 15%	H.influenza	None	None	0.7	65	↑
48	115	Neut. 55%,L 45%	No growth	None	None	0.25	25	↑
30	110	Neut.60%,L 40%	Pneumococcus	GPC in pairs	None	0.65	50	↑
600	225	L 85%,M 15%	No growth	None	None	0.02	24	↑
40	110	poly 85%,L 15%	No growth	None	None	0.55	45	↑
90	100	L 75%,M 25%	No growth	None	None	0.04	13	↑
58	220	L 60%,poly 40%	No growth	None	None	0.04	10	↑

,Group B Strep.-Group B Streptococcus, GPC-Gram positive cocci,hsCRP-highly sensitive c reactive protein,Vi-Viral,Py-Pyogenic

;

Bld C&S	Outcome			Final diagnosis
	complete recovery	sequelae	Death	
No growth	Yes	Nil	No	Py
No growth	No	Yes	No	Py
No growth	No	Yes	No	Vi
No growth	Yes	Nil	No	UD treated as Py
No growth	No	Nil	yes	Vi
Pneumococcus	No	Nil	yes	Py
No growth	No	Yes	No	VI
No growth	No	Yes	No	Py
No growth	No	Yes	No	Tb
No growth	No	Yes	No	UD treated as Py
No growth	No	Nil	yes	Py
No growth	Yes	Nil	No	Vi
No growth	No	Nil	yes	Py
H.influenza	No	Yes	No	Py
Group B strep	No	Nil	yes	Py
No growth	Yes	Nil	No	Vi
No growth	Yes	Nil	No	Vi
No growth	Yes	Nil	No	Fungal
No growth	Yes	Nil	No	Py
No growth	Yes	Nil	No	Vi
No growth	No	Nil	yes	Py
Pneumococcus	Yes	Nil	No	Py
No growth	Yes	Nil	No	UD treated as Vi
No growth	Yes	Nil	No	Py
No growth	No	Yes	No	VI
H.influenza	No	Yes	No	Py
No growth	No	Nil	yes	Py
No growth	No	Yes	No	Tb
No growth	Yes	Nil	No	Vi
No growth	Yes	Nil	No	Vi
Pneumococcus	No	Yes	No	Py

No growth	No	Yes	No	Vi
No growth	No	Yes	No	UD treated as Py
No growth	No	Nil	yes	Py
Group B strep	No	Yes	No	Py
No growth	No	Yes	No	Vi
No growth	Yes	Nil	No	UD treated as Py
No growth	No	Yes	No	Py
No growth	Yes	Nil	No	Vi
No growth	No	Yes	No	UD treated as Py
Pneumococcus	No	Yes	No	Py
No growth	Yes	Nil	No	Vi
No growth	No	Yes	No	Vi
No growth	No	Nil	yes	Py
No growth	No	Yes	No	UD treated as Py
No growth	No	Nil	yes	Py
No growth	No	Yes	No	Tb
Meningococcus	No	Nil	yes	Py
No growth	No	Yes	No	Vi
No growth	Yes	Nil	No	UD treated as Vi

INTRODUCTION

The salutary effect of the advent of highly effective antimicrobials is represented by the available history of pyogenic meningitis since the early 18th century till date. The prognosis of the patients with bacterial meningitis in those times was dismal.

In 1920, 77 children died due to Hemophilus influenza in the Boston hospital and the outcome of Pneumococcal meningitis was equally bad, which killed as many as 300 patients. In early 1900, the mortality rate associated with

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INTRODUCTION The salutary effect of the advent of highly effective antimicrobials is represented by the available history of pyogenic meningitis since the early 18th century till date. The prognosis of the patients with bacterial meningitis in those times was dismal. In 1920, 77 children died due to Hemophilus influenza in the Boston hospital and the outcome of Pneumococcal meningitis was equally bad, which killed as many as 300 patients. In early 1900, the mortality rate associated with meningococci was 85%. Given its dire consequences, the prompt diagnosis and the timely identification of the species causing meningitis is crucial, which is challenged by the various confounding factors that...