"CLINICAL PROFILE OF ACUTE FEBRILE ENCEPHALOPATHY IN ADULTS AT A RURAL SETUP"

By

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IN

GENERAL MEDICINE

Under the Guidance of

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ABSTRACT

BACKGROUND:

"Acute febrile encephalopathy" is a term commonly used to identify this condition in which altered mental status either accompanies or follows a short febrile illness. It is a common condition leading to hospital admissions in both adults and children in India. Similar studies were undertaken in north India to establish the etiology and prognosis of patients with acute febrile encephalopathy, So an attempt was made to study the etiology and prognosis of patients with AFE in this part of South India, Karnataka. Identification of the etiology helps in instillation of early treatment and better outcomes of the patients, hence this study was undertaken to study the etiology & outcome of patients with acute febrile encephalopathy who presented to our hospital with history of fever and altered sensorium.

OBJECTIVES OF THE STUDY:

PRIMARY OBJECTIVE

1. To study the clinical profile and in hospital course and outcome of patients presenting as febrile encephalopathy.

SECONDARY OBJECTIVE

1. To formulate etiological diagnosis of patients presenting as febrile encephalopathy.

MATERIALS AND METHODS:

A Prospective observational study is done in patients aged 18 years or above who presented with Acute Febrile Encephalopathy for a period of one year from 01 February 2013 to 01 February 2014.

All the non-infectious causes of unconsciousnesswere excluded and then only a diagnosis of AFE was considered. Cerebrospinal fluid (CSF)analysis and imaging of brain was done to determine the possible etiology.

RESULTS:

A Total of 100 patients of acute febrile encephalopathy was studied, the most common cause was 41 (41%) with Tubercular meningitis,followed by Cerebral malaria 26 (26%), Acute Viral encephalitis18(18%)(Japanese B encephalitis in 5.6%, herpes simplex virus encephalitis in 16.6%, and other undetermined viral etiology in 77.7%) and Pyogenic meningitis 15 (15%).

In the study it was observed that 40% (6 patients out of 15) with Pyogenic meningitis, 22.2% (4 out of 18) with Acute Viral encephalitis, 12.1% (5 out of 41) with Tubercular meningitis and 7.6% (2 out of 26) with Cerebral Malaria cases had mortality.

CONCLUSIONS:

1. In this study Tubercular meningitis is being the most commonest cause (41%), followed by Cerebral malaria (26%), Viral encephalitis (18%) and Pyogenic meningitis (15%).
2. There is a high incidence of cerebral malaria as it is an endemic area and early detection and treatment helps in improving the outcome of patients.
3. Patients with Pyogenic meningitis had the worst prognosis in terms of survival outcomes
4. Patients with Cerebral malaria had the best prognosis in terms of survival outcomes.
5. Our study demonstrates that acute febrile encephalopathy in adults is a heterogeneous syndrome with primary CNS infections being the commonest etiology.

Key Words : Acute febrile encephalopathy, Tubercular meningitis, Acute Viral encephalitis, Cerebral malaria

LI ST OF ABBREVIATIONS

AFE	Acute febrile encephalopathy
TBM	Tubercular meningitis
AVE	Acute Viral encephalitis
CNS	Central nervous system
ABM	Acute Bacterial meningitis
CSF	Cerebrospinal fluid
CM	Cerebral malaria
P.F	Plasmodium falciparum
EEG	Electroencephalogram
HRP	Histidine rich protein
CBC	Complete blood count
GLUT	Glucose transporter
AFB	Acid fast bacilli
LP	Lumbar puncture
MRI	Magnetic resonance imaging
CT	Computed tomography
RBC	Red blood cell
MRC	Medical research council
ICP	Intracranial pressure
SAS	Sub arachnoid space
HSV-1	Herpes simplex virus 1
HSV-2	Herpes simplex virus 2
VZV-	Varicella zoster virus
EBV-	Epstein barr virus
CMV	Cytomegalovirus
HSE	Herpes simplex encephalitis
JE	Japanese encephalitis
HIV	Human immunodeficiency virus
SAE	Sepsis associated encephalopathy

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INTRODUCTION

Infectious diseases remain a major cause of death and disability for millions of people around the world, despite decades of dramatic progress in their treatment and prevention.

Each infectious agent can cause a spectrum of illnesses, which challenges the physician's diagnostic skills.

The central nervous system (CNS) may appear protected from perturbations in the environment by a blood brain barrier – a system of tight junction around capillaries that resist the entry of pathogens, inflammatory cells and macromolecules into the subarachnoid space and the brain. However, the barrier fails to resist the intensity of the microbial world and its presence also cause difficulty in the delivery of antimicrobial agents in adequate concentrations.

As vital tissues are involved, CNS infection can cause devastating sequelae and in some cases may result in both neurological and medical emergencies.

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

Meningitis is a burning problem of the world. Meningitis is the result of various etiologies like tubercular, pyogenic or aseptic. Of these, tuberculous meningitis is common infectious disease of CNS in developing countries like India, and also a major global health problem even in developed world due to increasing number of people infected with HIV[2,3] .

"Acute febrile encephalopathy" is a term commonly used to identify this condition in which altered mental status either accompanies or follows a short febrile illness. It is a common condition leading to hospital admissions in both adults and children in India. Central nervous system (CNS) infections are the most common cause of non-traumatic coma.

Acute febrile encephalopathy is a heterogeneous syndrome. There is a tendency amongst clinicians and investigating agencies to jump to the conclusion that any illness with fever, altered sensorium, and seizures in young children is 'encephalitis' and all such episodes are due to viruses. This is not the case always.

The differentiation of acute encephalitis cases from acute encephalopathy is at times quite difficult but certain distinguishing features are worth mentioning.

Presence of low serum glucose, markedly raised liver enzymes, absence of pleocytosis on CSF examination, normal brain scans (except for brain edema), and no residual neurological deficit after recovery are few distinguishing features that should alert a treating clinician to explore a diagnosis other than acute viral encephalitis. Careful consideration of these finer points of differentiation between the two clinical entities is often necessary to prevent clinicians from pursuing an exhaustive search for a putative virus that never exists.

Acute febrile illness with altered mental status is a common complaint of the patients who have presented to hospital in this part of South Karnataka. An attempt has been made to study the etiology & outcome of acute febrile encephalopathy.

OBJECTIVES OF THE STUDY

PRIMARY OBJECTIVE

To study the clinical profile and in hospital course and outcome of patients presenting as febrile encephalopathy.

SECONDARY OBJECTIVE

To formulate etiological diagnosis of patients presenting as febrile encephalopathy.

REVIEW OF LITERATURE

Historical Review

The history of meningitis dates back to 300 BC when its existence was shown by Edwin Smith Papyrus. The first clinical recognition of cerebrospinal fluid (CSF) is attributed to Gallen's account in the second century, of a clear fluid residue in the ventricles of living brain in animal studies.

1661: Thomas Willis an English physician was probably the first to describe an outbreak of bacterial meningitis.

1764: Domenico Contugno gave a clear and complete description of the CSF. He was the first to recognize the continuity between the cerebral and spinal fluids.

1805: Veiusseux redefined bacterial meningitis and coined the term "Malignant Purpuric Fever" as a first clinical description for meningitis.

1806: Danielson & Mann have given the first account of cerebrospinal meningitis in American literature.

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

1882: The tubercle bacilli was discovered by Robert Koch.

1887:Weischselbaum described N. meningitides as the causative agent of meningitis.

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

1891:Quincke devised the diagnostic lumbar puncture

1893:Licktheim isolated tubercle bacilli from CSF.

1893: Walter showed that the blood CSF barrier to bromide is altered in T.B. meningitis.

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

1932: Burr & Finley studied the role of immunity in tubercular meningitis by injecting tubercle protein in the cisterns of controls and hypersensitive animals.

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

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

1958: Udani and Dastur showed that TB meningitis could present in the form of encephalopathy.

1969: Dastur and Wadia showed that TB meningitis could present as spinal arachnoiditis.

1980: Antonine Jesse noticed that TB meningitis was more often associated with TB of other organs.

ANATOMY AND PHYSIOLOGY

The central nervous system is enveloped by the skull and vertebral column and meninges and connective tissue coverings. Meninges are named from within as the dura mater, the arachnoid and pia mater.

Dura mater:

This is the outermost covering, consisting of thick and fibrous membrane and serves as the internal periosteum of the bones of the skull to which it is closely applied. The inner surface is covered with a layer of endothelial cells. Sheaths of dura mater extend outwards for a short distance as covering for cranial nerves as they pass through their respective foramina.

At its superior border it splits into two layers to contain superior sagittal sinus and its lower free border contains the inferior sagittal sinus. The tentorium cerebelli forms partition between the posterior and middle fossae of the skull. Its free border surrounds the midbrain, and is attached to the occipital and parietal bones. The posterior parts of its attached border splits to enclose the transverse sinus and the anterior part encloses the superior petrosal sinus.

The spinal dura forms a lining to the vertebral canal from which it is separated by epidural space containing fatty tissues and venous plexus. The dura extends to the second or third sacral vertebra.

The space between dura mater and the spinal canal is known as ‘epidural space’ and the space between dura mater and arachnoid mater is known as subdural space and it is devoid of CSF[4].

Arachnoid mater:

The arachnoid is a similar membrane, lying between the dura and piamater and bridges over the sulci. The space between the arachnoid and piamater is called the subrachnoid space and it contains the CSF. Its expansions are known as the subarachnoid cisterns. Arachnoid is a delicate avascular membrane. It extends over the spinal cord upto the second sacral vertebra.

Cerebello-medullary cistern is between the inferior surface of the cerebellum and the posterior surface of the medulla. The sub arachnoid space extends into the nervous system as the perivascular space. The subarachnoid space communicates with fourth ventricle through foramen of Magendi (Median aperture) and foramen of Luschka (two lateral apertures).

The dilatations of subarachnoid space in the cranium are known as cisterns, such as cisterna magna, cisterna pontis and cisterna interperpendicularis.

Subarachnoid space also continues around the optic nerves upto the eye ball. The arachnoid granulations are small fleshy elevations present in the vicinity of superior and transverse sinuses.

The Pia mater:

It is the inner most layer which is very thin and closely covers the brain tissue and dips into the sulci and fissures. It is fused with endothelial cells. The space between the arachnoid and pia mater is called perivascular space which contains CSF. It ensheaths all cranial and spinal nerves.

The dura mater is known as pachymeninx, the arachnoid and pia as the leptomeninges. Infection of dura matter is called pachy meningitis and that of arachnoid and pia as leptomeningitis or simply as meningitis.

Blood supply: Meninges are supplied by, a) occipital, b) ascending pharyngeal, c) vertebral, d) maxillary, e) lacrimal, f) anterior and posterior ethmoidal arteries through their meningeal branches.

Venous drainage is by their accompanying veins of corresponding arteries which ultimately drain into the jugular veins.

Nerve Supply: Is mainly by meningeal branches, recurrent branches, tentorial branches, middle meningeal and meningeal ramices of trigeminal nerve.

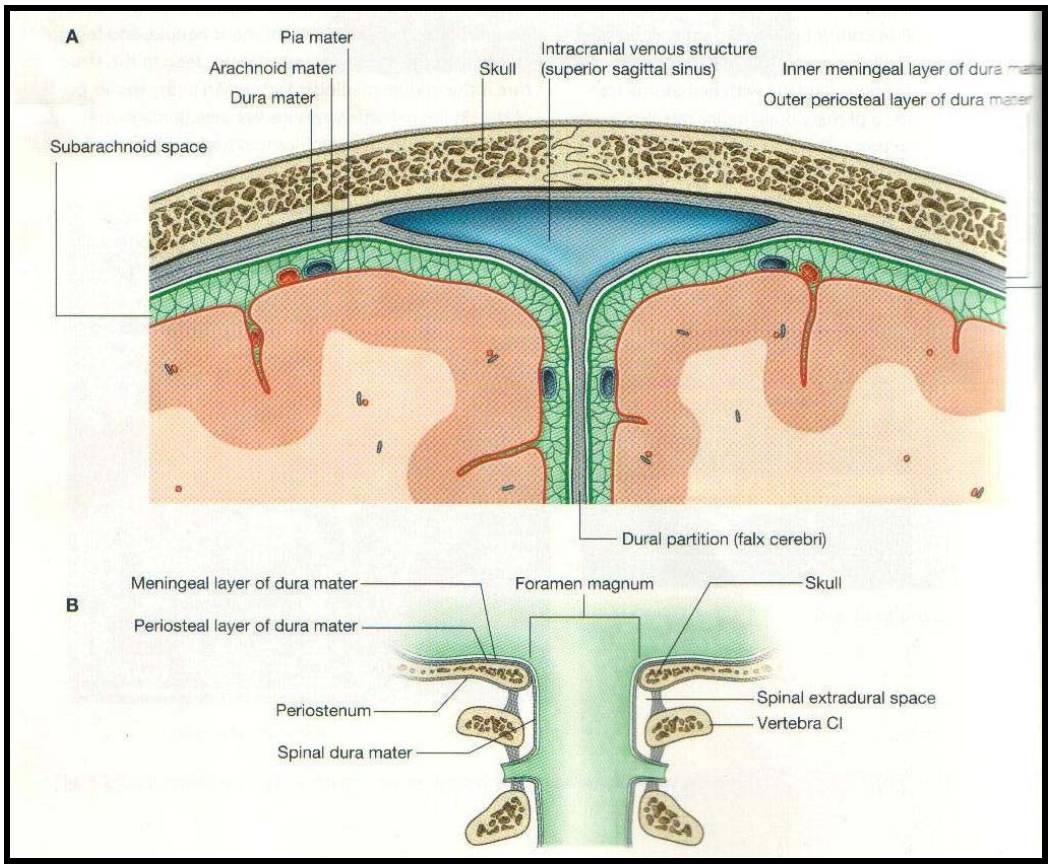


Fig.1: Cranial meninges

(A) Superior coronal view (B) Continuity with the spinal meninges

Choroid plexus:

Choroid plexuses are present in the ventricular cavities and are lined by ependyma. They are protrusion of tufts of arteries lined by piamater into the ventricles. They are responsible for formation and secretion of CSF.

Physiology of Cerebrospinal fluid

Claude Bernard described blood and lymph as the mileu intern of the organism. In central nervous system there are no lymphatics and there exists blood brain barrier. The cerebrospinal fluid can be considered as lymph of the brain. The brain and the spinal cord are bathed by CSF in subarachnoid space which is continuous over brain and spinal cord.

Site of Production - Circulation and Absorption:

The fact that CSF is actively secreted by the choroid plexus was first demonstrated by Dandy and Blackfan in 1914.

Choroid plexus are a highly vascular structure formed by piameter and ependyma when they came near along the margin of ventricle. It projects into ventricles as convoluted cauliflower like ribbon and carries a combination of active transport and filtration that yields the fluid having much less protein than plasma.

Several evidences support the conclusion that CSF is not merely a protein free transudate of plasma. These are as follows:

a. During neurosurgical operation droplets of fluid can be seen on the inner surface of choroid plexus.
b. Differences in core of cations and anions cannot be explained by pure physiochemical mechanism.

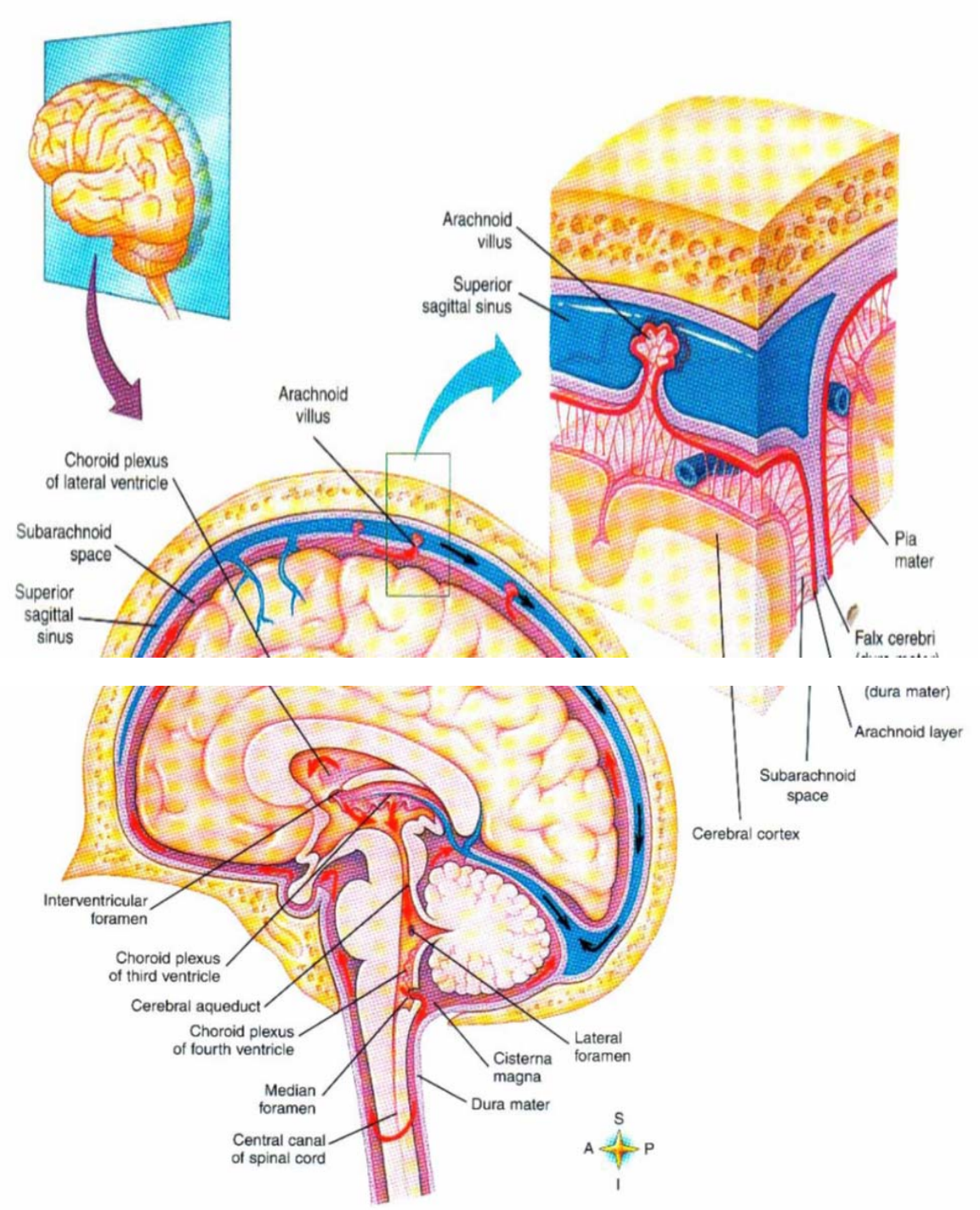


Fig.2: Flow of cerebrospinal fluid

CSF that is formed by the plexuses of the lateral ventricles passes through interventricular foramina into third ventricle. Then the fluid flows through the cerebral aqueduct into the fourth ventricle, which it leaves by the median and two lateral foraminae (foramina of Magendie and Lushka) of the fourth ventricle to reach the subarachnoid space.

The CSF probably receives a contribution from the perivascular space, and also from the lymphatics of cranial and other peripheral nerves. After bathing the surface of the spinal cord and the base of the brain it passes upwards over the convexity of the cerebral hemispheres, to be absorbed into the intracranial venous sinuses through the microscopic arachnoid villi which protrude into the sinuses.

Volume and Composition of CSF

Volume of CSF is around 150 ml or about 8% of the total CNS cavity volume. It is believed to be produced at a rate of 500-600 ml per day or about 0.4 ml/ minute. It undergoes rapid turnover. Principal site of production is choroid Plexus. Site of absorption is through arachnoid villi.

CSF has the following constituents

Protein Ventricular 5-15 mg/dl

Cisternal 15-25 mg/dl

Lumbar 14-45 mg/dl

Glucose 44-100 mg/dl

Chloride 725-750 mg/dl

Phosphorus 7.31 (at arterial PH of 7.41)

CSF also contains cells varying from 0-5 cells per mm3 all of which are lymphocytes.

Enzymes present in CSF are AST, LDH and CPK.

Normal Pressure of CSF is 100-200 cm of H2O

Functions of C.S.F.

1. It mechanically protects the central nervous system from jerks and shocks.
2. It regulates the intracranial pressure.
3. Acts as a support to the venous sinuses in different postures.
4. CSF plays a part in the nutrition and metabolism of the nervous system.
5. The pH of CSF is about 7.31 which probably plays a part in central regulation of respiration.
6. Involved in the distribution of hypophyseal hormones within the brain and the clearance of hormones from the brain to the blood.

MENINGITIS

Definition

Meningitis is an infection within the subarachnoid space. It is associated with a central nervous system inflammatory reaction that may result in decreased consciousness, seizures, varied intracranial pressure and stroke. The meninges, the subarachnoid space… 1 and the brain parenchyma are all frequently involved in the inflammatory reaction.

ENCEPHALITIS

Definition

It is an inflammation of the brain tissue due to infection. Most often caused by viruses that pass into blood stream and then into cerebral spinal fluid, leading to destruction of neural cells and inflammation of brain parenchyma.

It may also result from a viral-mediated inflammatory response in the brain following an acute, systemic infection. In febrile illness, encephalopathy may result from directly or systemic complications like hypoglycaemia, hypovolemia, hyperpyrexia, hypoxia, anaemia, hepatic or renal failure and bleeding may contribute to its pathogenesis.

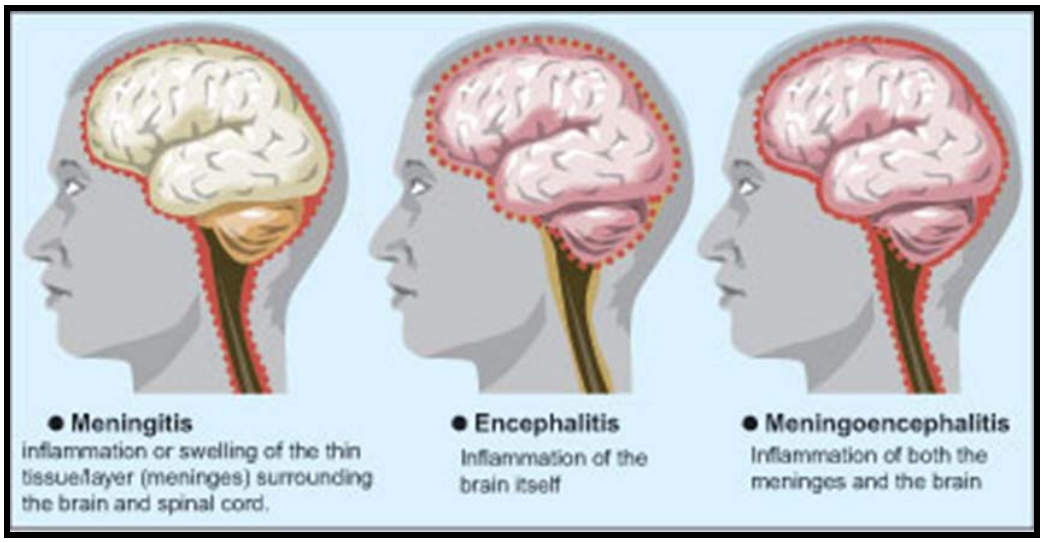


Fig3.Diagram of meningitis and encephalitis

Types of meningitis:-

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

Lymphocytic meningitis:

The most common cause of lymphocyte predominant meningitis is tuberculosis in developing world, other causes are syphilis, lymes disease, crypotococcosis, brucellosis, and other fungal infections etc.

Out of all these, tuberculosis remains a major public health problem, mostly seen in age group of 15-59 years. But increasing incidence of human immune deficiency virus (HIV), there is a potential for re-emergence of tuberculosis as a significant public health problem in the developed countries as well.[5]

It is estimated that 5-10% of all tuberculosis have central nervous system involvement. Of the various manifestations of CNS tuberculosis, meningitis is the most common (70-80%) followed by tuberculoma.[6]

Risk factors for the tuberculosis meningitis include recent acute infectious disease in children, alcoholism, diabetes, malignancy, chronic corticosteroid administration and AIDS.[7]

The majority of cases of tuberculosis meningitis is due to mycobacterium tuberculosis with M.bovis being responsible for less than 5% of cases[8]. Despite the frequency of Mycobacterium avium intracellulare in AIDS cases, few cases of tuberculous meningitis due to nontuberculous mycobacterium have been reported.[9]

Pathogenesis

Tuberculous meningitis arises as a complication of Tuberculosis elsewhere in the body even though extracranial focus is not identifiable in majority of cases.

Two stages in the evolution of tuberculous meningitis are described here

i. Initial seeding in the brain or meninges by haematogenous dissemination of bacilli during primary infection or later from ruptured caseous granuloma.
ii. Rupture of one of the above subpial caseous tuberculous foci in brain called Rich Focus.

The other mechanisms of tuberculous meningitis include

a. Hematogenous dissemination during Primary infection / miliary tuberculosis.
b. Direct extension from adjacent extracranial sites like mastoiditis tuberculosis of spine or skull bones.
c. Intracranial lymphatic spread from cervical lymphoids.

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

Pathology

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

a. Inflammatory meningeal exudates.
b. Vasculitis of arteries traversing the exudate.
c. Disturbance of cerebrospinal fluid flow causing hydrocephalus.

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

Hydrocephalus develops early and is much more frequent and severe in children than it is in adults.[10]

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

The severity of meningitis is inversely related to the immune status of the individual. Tuberculous meningitis is usually less severe in BCG vaccinated children.[11]

Clinical Features

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

Medical Research Council (MRC) staging of TBM.[12,13]

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

Diagnosis

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

CSF analysis plays a pivotal role in the diagnosis of tuberculous meningitis.

Opening pressures are often but not invariably elevated.[14]

Classically the CSF in tuberculous meningitis is clear, colourless and may show a pellicle or cobweb clot. On standing high protein levels can make CSF appear xanthocromic. The protein levels in CSF usually range from 100-500 mg%.[15] Initial level of more than 300mg% correlates with poor prognosis. In advanced cases due to spinal block, xanthochromia can develop with protein content of 1000-1500mg%.

CSF glucose is below 40mg per dl or 50% of the parallel blood sugar value, though it is never as low or absent as in pyogenic meningitis.[16] CSF chloride value does not have any diagnostic or prognostic value.

Microscopic examination of CSF reveals pleocytosis usually not exceeding 500 cells per mm3. Majority of cells are lymphocytes. In the early stages polymorphonuclear reaction can be observed which is replaced by lymphocytes in a period of weeks if untreated.

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

In patients with AIDS and tuberculous meningitis CSF protein may be normal and occasionally acellular.[17]

Contemplated confirmatory diagnostic tests

These include tests based on detection of the mycobacterium

i. CSF smear for AFB

ii. CSF culture for AFB

Demonstration of AFB in CSF is the single most important procedure for a definitive diagnosis. CSF smear for AFB is positive in 5-37% cases and the CSF culture for AFB is positive in 40-80% cases.[15,17,18,19]

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

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

A variety of PCR methods have been developed for detection of specific sequences of M. tuberculosis and other mycobacteria.

A PCR assay system for tuberculosis, which is commercially available[20] has been found to be reproducible, sensitive as well as specific.[21]

As compared to 5-20 percent positivity with demonstration of AFB and mycobacterial cultures, PCR has been found to be positive in 50-70 percent of specimens from cases having cardinal features as well as biochemical/ cytological evidence of neurotuberculosis.[22,23,24]

Radioactive (82 Br) ammonium bromide test may be of assistance in diagnosis of blood / CSF bromide ratio 24 hours after oral administration of 0.6 micro curie per kilogram of the radioactive substance. If it is less than 1.6, it suggests the diagnosis. In other Central Nervous System infections the ratio is more than 2.

Management

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

Treatment regimen

The world health organization…43 put CNS tuberculosis under treatment category 1 and recommended initial phase therapy {2 months} with isoniazid rifampicin, ethambutol and pyrazinamide followed by continuation phase (4 months) with isoniazid and rifampicin.

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

Duration of therapy

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

The current recommendation is that tuberculous meningitis be treated for oneYear[25] or 9 month.[26] Though preliminary reports of the adequacy of a six month treatment are now available, the incidence of the neurological sequelae in these reports makes it wise to continue therapy for 12 months.

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

Syphilitic meningitis:

The major clinical categories of symptomatic neurosyphilis include meningeal, meningovascular, and parenchymatous syphilis. For meningeal syphilis the onset of symptoms usually occurs within one year of infection. It may involve either the brain or the spinal cord, and patients may present with headache, nausea, vomiting, neck stiffness, cranial nerve involvement, seizures, and changes in mental status.[27]

Patients presenting with uveitis or iritis frequently have meningeal syphilis.

The CSF shows pleocytosis(>5 white blood cells/cmm), increased protein concentration, and VDRL reactivity. The CSF VDRL is highly specific but is insensitive. CSF-FTA test may be used to rule out neurosyphilis[28]

Neurosyphilis is treated with intravenous penicillin for 10-14 days[29]

Cryptococcal meningitis:

Cryptococcus neoformans, a yeast like fungus, is the etiological agent of cryptococcosis. Infection is acquired by inhalation of aerosolized infectious particles.

Cryptococcosis usually presents clinically as chronic meningoencephalitis.

CNS involvement usually presents as signs and symptoms of chronic meningitis such as headache, fever, lethargy, Cranial nerve palsies etc[30]

The classical CSF abnormalities are lymphocytic pleocytosis, elevated protein, and visualization of fungal capsule with India ink preparation or detection of cryptococcal antigen test. The condition is treated with intravenous amphotericin-B with or without fluconazole[31]

Neutrophilic meningitis:

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

Bacterial meningitis:

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

The bacterial meningitis is the most common form of suppurative CNS Infection.

Currently, the organisms most commonly responsible for community acquired bactereial meningitis are Streptococcus pneumonia, N. Meningitides, group B streptococci and Listeria monocytogenes[32]

S.pneumoniae is the most common cause of meningitis in adults >20 years of age. The predisposing conditions that increase the risk of pneumococcal meningitis are pneumococcal pneumonia, sinusitis or otitis media, alcoholism, diabetes and splenectomy. Mortaliy remains 20% despite antibiotic therapy[33]

N.meningitidis most commonly seen in age group of 2-20 years. The presence of petechial or purpuric skin rash can provide an important clue to the diagnosis of meningococcal disease. Individuals with deficiencies of any of the complements including properdin are highly susceptible to meningococcal infections[34]

L.monocytogenes is an important cause of meningitis in neonates, but it has been reported with increasing frequency in individuals >50 years of age.

Staphylococcus aureus and coagulase-negative staphylococci are common causes of meningitis the occur following invasive neurosurgical procedures.

Most of bacteria initially colonize the nasopharynx by attaching to nasophyaryngeal epithelial cells, then invade the intravascular space by creating separations in the apical tight junctions of columnar epithelia cells.

Bloodborne bacteria can reach the intraventricular choroid plexus, directly infect choroid plexus epithelial cells and gain access to the CSF. Bacteria are able to multiply rapidly within CSF because of the absence of effective host immune defence.

A critical event in the pathogenesis of bacterial meningitis is the inflammatory reaction induced by the invading bacteria. Much of the pathophysiology of bacterial meningitis is a direct consequence of elevated levels of CSF cytokines and chemokines.

Meningitis can present as either an acute fulminant illness that progresses rapidly in a few hours or as a subacute infection that progressively worsens over several days. The classical clinical triad of meningitis is fever, headache, and nuchal rigidity. A decrease level of consciousness occurs in >75% of patients. Nausea, vomiting and photophobia are also common complaints[35]

The classical CSF abnormalities in bacterial meningitis are polymorphonuclear leukocytosis, decreased glucose concentration, CSF/serum glucose ratio < 0.4, elevated protein. The mainstay of treatment is antibiotic therapy[36]

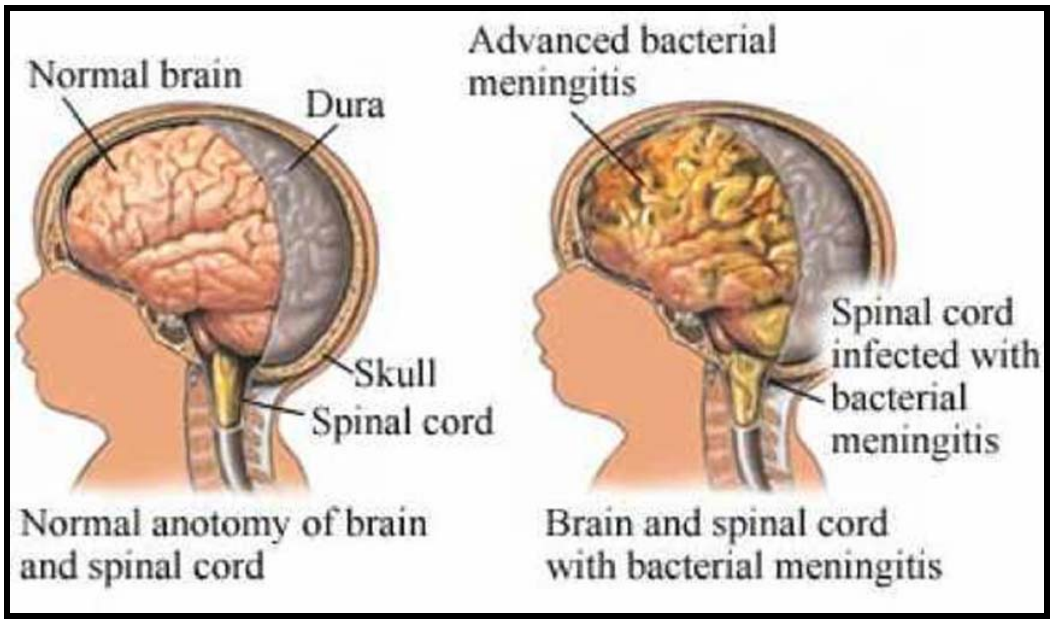


Fig 4. Diagram of bacterial meningitis

Aseptic meningitis:

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

The most important viruses are enteroviruses (coxsackieviruses, echoviruses, human enteroviruses 68-71), herpes simplex virus-2, arthropod borne viruses, and HIV etc[36,37]

Patients with viral meningitis usually present with headache, fever, and signs of meningeal irritation coupled with inflammatory CSF profile.

The typical profile is a lymphocytic pleocytosis as it is seen with other lymphocytic (tuberculosis), with normal glucose concentration, normal or mildly elevated protein level.[38]

As a rule, a lymphocytic pleocytosis with a low glucose concentration should suggest fungal, tuberculous or non-infectious (sarcoid, neoplastic) meningitis.

Though oral or intravenous acyclovir may be of benefit in patients with meningitis caused by HSV-1 or -2 and in cases of severe EBV or VZV infection, mainstay of therapy is supportive.

EPIDEMIOLOGY

Acute Bacterial Meningitis

The annual incidence of bacterial meningitis is more than 2.5 cases per 1,00,000 population in the united States.[39] More than 2000 deaths due to bacterial meningitis are reported annually in the United States. The disease is more common and the mortality higher in the developing countries like India.

The epidemiology of bacterial meningitis has changed significantly in recent years reflecting a dramatic decline in the incidence of meningitis due to Haemophilus influenzae, and a smaller decline in that due to Neisseria meningitides, following the introduction and increasingly widespread use of vaccines for both these organisms.

The prognosis of bacterial meningitis is critically dependent on a rapid causal diagnosis and implementation of prompt treatment. However, clinical and biochemical parameters available within the few hours that follow patients admission are not reliable enough, except when bacteria are to be found in the cerebrospinal fluid under the microscope.

Therefore, the initial treatment of acute meningitis is most of the time presumptive. The definitive diagnosis, however difficult, is often established when the therapeutic management has already been initiated. The use of biological markers, especially lymphokines and acute-phase proteins, has been proposed to facilitate the accuracy of the initial diagnosis.

Tuberculous meningitis (TBM)

It is still one of the common infections of central nervous system (CNS) and poses significant diagnostic and management challenges, more so in the developing world.[40] Despite modern antituberculosis chemotherapy, 20% to 50%[41] of patients still die, and many of the survivors have significant neurological deficits. With the lack of early diagnosis, fatality remains high, sequelae may be distressing and disabling in the non-fatal cases. Death from TBM is strongly associated with delays in diagnosis and treatment.

Disease Burden

Global burden of tuberculosis is still high, particularly in developing countries; and globally, there were an estimated 9.27 million new cases (139 per 100,000 population) of tuberculosis in 2007, and the number of prevalent cases was 13.7 million (206 per 100,000 population).[42] The incidence of CNS tuberculosis generally reflects the incidence and prevalence of tuberculosis in the community. About 10% of patients who have tuberculosis develop CNS disease.[43] HIV infection predisposes to the development of extrapulmonary tuberculosis, particularly tuberculous meningitis.[44]

With 206 per 100,000 prevalent cases of tuberculosis in 2007[40] and the projected incidence of cases of CNS tuberculosis being 20.6 per 100,000 population in the year 2007, most of it would be in the high-burden countries.

Incidence rates of tuberculous meningitis are age specific and range from 31.5 per 100,000 (<1 year) to 0.7 per 100,000 (10-14 years) in the Western Cape Province, South Africa.[45] The estimated mortality due to tuberculous meningitis in India is 1.5 per 100,000 population.[46] HIV co-infection is associated with higher complication and case fatality rates.[47,48]

Cerebral malaria

It is the most severe neurological complication of infection with Plasmodium falciparum malaria. It is a clinical syndrome characterized by coma and asexual forms of the parasite on peripheral blood smears. Mortality is high and some surviving patients sustain brain injury which manifest as long-term neuro-cognitive impairments.

Falciparum malaria is a leading cause of ill health, neuro-disability and death in tropical countries. Although 40% of the world's population is at risk, most transmission occurs in sub-Saharan Africa where children under the age of 5 years are most affected and the incidence of disease declines in older children with increasing immunity. In South-East Asia, malaria occurs more commonly in adults but the clinical features are different.[49]

Every year, there are over 500 million clinical cases. One percent of symptomatic infections may become complicated and develop into severe malaria. Severe malaria may manifest as anemia, hypoglycemia, metabolic acidosis, repeated seizures, coma or multiple organ failure and is estimated to cause over one million deaths annually.[49] Cerebral malaria is the most severe neurological manifestation of severe malaria. With an incidence of 1,120/100,000/year in the endemic areas of Africa, children in this region bear the brunt. Peak incidence is in pre-school children and at a minimum, 575,000 children in Africa develop cerebral malaria annually[50]. Recent reports however suggest that the incidence of severe malaria is on the decline.[51,52]

Acute viral encephalitis (AVE)

It is often an unusual manifestation of common viral infections and most commonly affects children and young adults; it can lead to considerable morbidity and mortality. Epidemiologic studies estimate the incidence of VE at 2.5–8.8 per 100000 persons per year. However the annual incidence of VE is most likely underestimated, especially in developing countries where there are problems with pathogen detection. Very few studies of VE have emanated from India, although it can be considered the epicenter of many emerging viral diseases.

Every day new viruses are being associated with encephalitis of varying severity. It would be useful to harbor a strong clinical suspicion for an unusual viral etiology in cases of both sporadic as well as epidemics of encephalitis. Japanese B

encephalitis virus (JEV) is an emerging pathogen in North India and has entrenched itself firmly in the eastern parts of Uttar Pradesh.

In temperate climates, there is a substantial increase in cases during the summer and early fall months, reflecting the seasonal predominance of enterovirus and arthropod-borne virus (arbovirus) infections.

Many times even after a detailed diagnostic workup one may not be able to reach to a definitive diagnosis. Nevertheless, a detailed examination and workup is warranted as conditions like Herpes simplex encephalitis (HSE) are eminently treatable.

ETIOLOGY

1. Bacteria causing meningitis

Streptococcus pneumoniae (pneumococcus): It is the most common cause of meningitis (50%) in adults > 20 years of age, accounting for nearly half the reported cases (1.1 per 1,00,000 persons per year).[39]

- N. Meningitis ~ 25%.
- Group B streptococci ~ 15%.
- Listeria monocytogens ~ 10%.
- H. influenza < 10%.

Less common causes include:

Staphylococcus aureus, coagulase negative staphylococci following invasive neurosurgical procedure.

- Enteric gram-negative bacilli in patient with chronic and debilitating diseases such as diabetes, cirrhosis, alcoholism, chronic urinary tract infections and can also complicate neurosurgical procedures, particularly craniotomy.

- Mycobacterium tuberculosis.
- Others – Borrelia burgdorferi, tropenoma pallidum, actinomyces, nocardia, brucella, leptospirosis, tropherema whippelii.

2. Viruses causing meningitis

Common	**Less common**	**Rare**
HIV	HSV-1	Adenoviruses
Enteroviruses	LCMV	CMV
Arboviruses	VZV	EBV
Parainfluenza,	Infuenza A,B	
HSV-2	Mumps,Rubella.	

3. Fungal causes of meningitis

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

4. Protozoal causes of meningitis

- Toxoplasma gondii.
- Trypanosoma gambiense.
- Trypanosoma rhodesiense.

5. Helminthic causes of meningitis

- Cysticercosis.
- Gnathostoma spinigerum.
- Angiostrongylus cantonensis.
- Baylisascaris procyonis.

6. Non-infectious causes

- Malignancy.
- Chemical compounds.
- Primary inflammation – CNS sarcoidosis.
- Vogt Koyanagi Harada Syndrome.
- Systemic Lupus Erythematosis.
- Behcet's syndrome.
- Chronic benign lymphocytic meningitis.
- Drug hypersensitivity.
- Wegener's Granulomatosis.

PATHOPHYSIOLOGY OF MENINGITIS

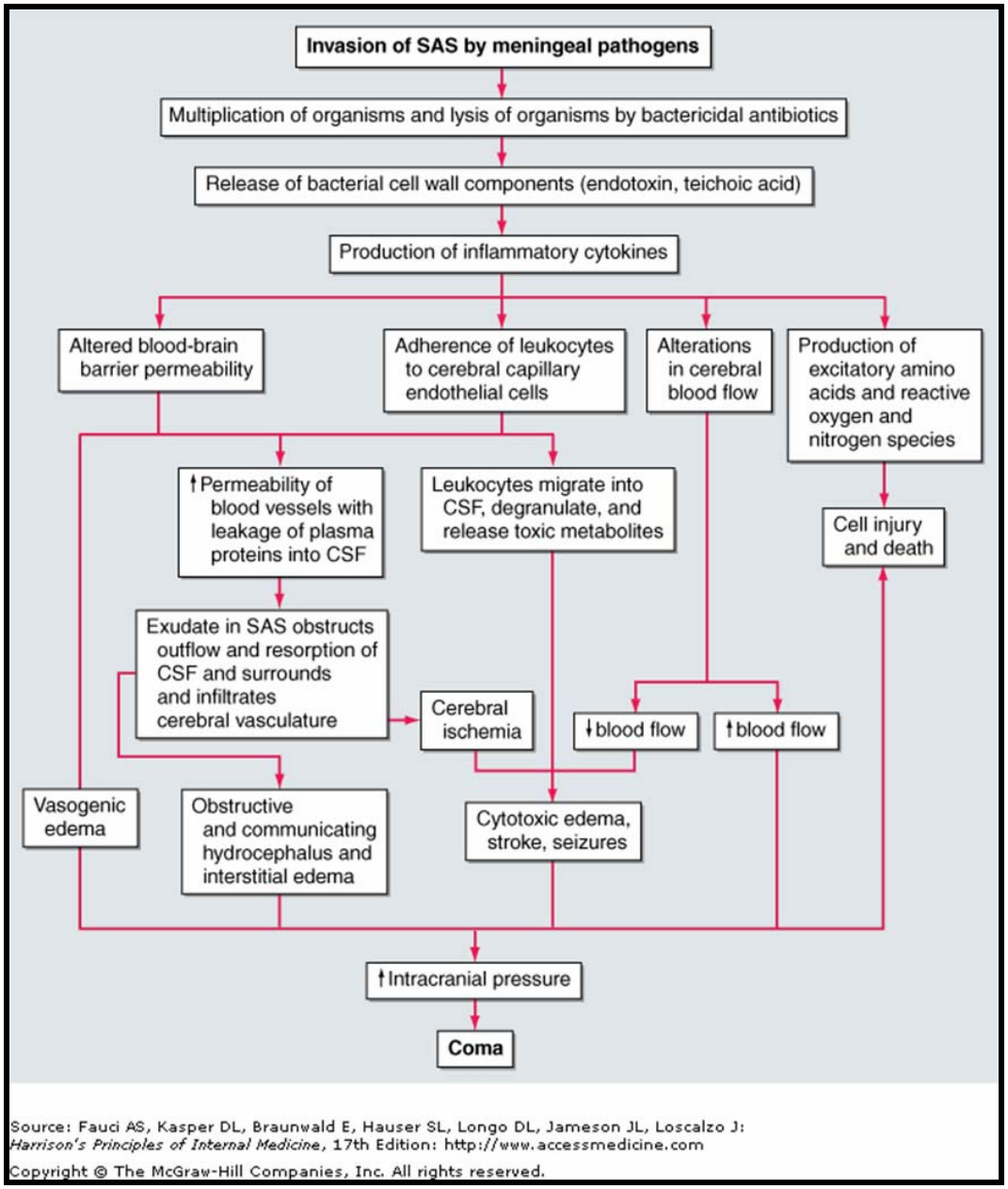


Fig 5: The pathophysiology of the neurologic complications of meningitis. SAS, subarachnoid space; CSF, cerebrospinal fluid

CLINICAL PRESENTATION

Meningitis can present as either an acute fulminant illness that can progress rapidly in a few hours, or as a sub acute infection that progressively worsens over several days.

The classic clinical triad of meningitis is fever, headache, and nuchal rigidity ("stiff neck").

Each of these signs and symptoms occurs in >90% of cases. Alteration in mental status occurs in >75% of patients and can vary from lethargy to coma. Nausea, vomiting, and photophobia are also common complaints.

Nuchal rigidity is the pathognomonic sign of meningeal irritation and is present when the neck resists passive flexion. Kernig's and Brudzinski's signs are also classic signs of meningeal irritation.

Seizures occur as part of the initial presentation of meningitis or during the course of the illness in up to 40% of patients. Focal seizures are usually due to focal arterial ischemia or infarction, cortical venous thrombosis with hemorrhage, or focal edema.

The rash of meningococcemia begins as a diffuse erythematous maculopapular rash resembling a viral exanthem, but the skin lesions of meningococcemia rapidly become petechial. Petechiae are found on the trunk and lower extremities, in the mucous membranes and conjunctiva, and occasionally on the palms and soles.

Raised intracranial pressure (ICP) is an expected complication of bacterial meningitis and is the major cause of obtundation and coma in this disease. More than 90% of patients will have a CSF opening pressure >180 mm H2O, and 20% have opening pressures >400 mm H2O.

Signs of increased ICP include a deteriorating or reduced level of consciousness, papilledema, dilated poorly reactive pupils, sixth nerve palsies, decerebrate posturing, and the Cushing reflex (bradycardia, hypertension, and irregular respirations).

The most disastrous complication of increased ICP is cerebral herniation. The incidence of herniation in patients with bacterial meningitis has been reported to occur in as few as 1% to as many as 8% of cases.

Tuberculous meningitis usually presents with headache, fever, vomiting, altered sensorium, and sometimes convulsions. It is diagnosed clinically with confirmation by microscopy, culture of cerebral spinal fluid, or the polymerase chain reaction test.

Disability in tuberculous meningitis is multifactorial. Some of the important causes of disability are persistent or progressive hydrocephalus, involvement of the optic nerves or optic chiasm in the supracellar region, vasculitis leading to cerebral infarcts and stroke, multiple cranial neuropathies, and arachnoiditis.

Disability related to antituberculous treatment most often occurs as ethambutol-induced toxic optic neuritis, which may be irreversible, or isoniazid related peripheral neuropathy.

Tuberculous meningitis can be classified according to its severity.

The British Medical Research Council (MRC) use three stages (MRC 1948):

Stage I (mild cases) is for those without altered consciousness or focal neurological signs;

Stage II (moderately advanced cases) is for those with altered consciousness who are not comatose and those with moderate neurological deficits (eg single cranial nerve palsies, paraparesis, and hemiparesis); and

Stage III (severe cases) is for comatose patients and those with multiple cranial nerve palsies, and hemiplegia or paraplegia, or both.

Viral meningitis usually results in a benign and self-limiting illness requiring no specific therapy. It is a much less serious illness than bacterial or tubercular meningitis, unless there is associated encephalitis, which is rare. It occurs with acute onset headache and irritability. The headache is usually the more severe feature. Failure of a patient with suspected viral meningitis to improve within 48 hours should prompt a reevaluation.

The clinical manifestations of severe malaria can be many and varied (Table-1). Other than cerebral malaria, the complications which need to be addressed urgently are severe anaemia, acute renal failure, acute lung injury, jaundice (and hepatic involvement), hypoglycaemia, and circulatory collapse with algid malaria.

Table 1. : Severe manifestations of P. falciparum malaria in adults.

Major criteria

1. Cerebral malaria (unarousable coma not attributable to any other causes).
2. Severe anaemia (haematocrit< 15% or haemoglobin< 5 g/dl).
3. Acute renal failure (urine output < 400 ml/ 24 hours in adults, or < 12 ml/kg/24 hours in children, failing to improve after rehydration; and serum creatinine > 265 μmol/1 i.e., > 3 mg/dl).
4. Pulmonary oedema or adult respiratory distress syndrome (ARDS).
5. Hypoglycaemia (whole blood glucose < 2.2 mmol i.e., < 40 mg/dl).
6. Circulatory collapse, shock, hypotension (systolic blood pressure < 50 mm Hg in children aged 1-5 years or < 70 mm Hg in adults), with cold, clammy extremities.
7. Spontaneous bleeding/disseminated intravascular coagulation.
8. Repeated generalised convulsions (more than two episodes in 24 hours).
9. Acidaemia (arterial pH < 7.25) or acidosis (plasma bicarbonate < 15 mmol/1).
10. Macroscopic haemoglobinuria.

Minor criteria

1. Hyperparasitaemia (> 5% of RBCs are parasitised).
2. Hyperpyrexia (rectal temperature > 400 C).
3. Jaundice (Serum bilirubin > 50 mol/1 or > 3 mg/dl.).
4. Severe prostration.

DIAGNOSIS

When the clinical presentation is suggestive of meningitis, blood cultures should be immediately obtained and empirical antimicrobial therapy initiated without delay.

The diagnosis of meningitis is made by examination of the CSF. The need for cranial magnetic resonance imaging (MRI) or computed tomography (CT) prior to lumbar puncture remains a controversial issue and must be dealt with on a case-by-case basis.

In a patient with a normal level of consciousness and a neurologic examination with no evidence of papilledema or focal deficits, it is safe to perform lumbar puncture without prior neuroimaging studies.

If lumbar puncture is delayed in order to obtain neuroimaging studies, empirical antibiotic therapy should be initiated after blood cultures are obtained.

Antibiotic therapy for several hours prior to lumbar puncture will not significantly alter the CSF white blood cell count or glucose concentration, nor is it likely to sterilize the CSF so that the organism cannot be identified on Gram's or AFB stain.

Increased ICP should be treated in patients with clinical signs of increased pressure, and lumbar puncture performed with a 22- or 25-gauge needle.

Only a minimum amount of CSF need be removed for analysis; ~3.5 ml of CSF is sufficient to obtain a cell count(1.0 ml), glucose and protein concentrations (1.0 ml), and Gram's stain, AFB stain and bacterial cultures (1.0 ml). If possible, an additional 0.5 to 1.0 ml should be saved.

Almost all patients with bacterial meningitis will ultimately have neuroimaging studies performed. MRI is preferred over CT because of its superiority in demonstrating areas of cerebral edema and ischemia.

In patients with bacterial meningitis, diffuse meningeal enhancement is often seen after the administration of gadolinium. Meningeal enhancement is not diagnostic of meningitis but occurs in any CNS disease associated with increased blood-brain barrier permeability.

Table 2: CSF Analysis

CSF Analysis	Bacterial meningitis	Tubercular meningitis	Viral Meningitis
Opening pressure	>180 mm H2O	>120 mm H2O	100-350 mmH2O
White blood cells	10- 10,000/microL, Neutrophil predominant	10- 1000/microL Predominantly lymphocytic	25-500/microL, lymphocytic pleocytosis
Red blood cells	Absent in non traumatic tap	Absent in non traumatic tap	Absent in non traumatic tap
Glucose	<40mg/dl	<40mg/dl	Normal
Protein	>45mg/dl	>45mg/dl	20-80mg/dl
Gram's stain	Positive in >60%	Negative	Negative
ZN Stain	Negative	May be positive in 37%	Negative
Culture	Positive in >80%	Positive in 56%	

The importance of measuring CSF Glucose and CSF Protein:

GLUCOSE:

Glucose is one of the physiologically important sugars present in significant concentrations in various body fluids including the CSF.

Glucose enters CSF via choroid plexus as well as by transcapillary movements into the extracellular fluid space of the brain and spinal cord, which is contiguous with the CSF. It does not enter the CSF solely in the ventricles.

The CSF glucose level at any moment is parallely related to changes in blood glucose level. In humans and in steady state, CSF glucose is about 60% of the blood glucose.

Brain tissue contains only about 20 mg/kg glucose in the steady state, this may explain low level of glucose in CSF due to its movement "down hill" into the tissues. Thus normally the brain serves as a "sink" for glucose derived from the blood (100mg/dl) and from CSF (60mg/dl).

Normal level of CSF glucose is between 45-80 mg/dl in patients with blood glucose of 70-120 mg/dl. Normal CSF: blood glucose ratio is 0.6. CSF : blood glucose ratio of <0.31 is seen in 70% of bacterial meningitis patients.[53]

Mechanism of glucose exchange between blood and CSF:

Glucose exchange between blood and CSF was first established by Fishman in1964 and later between blood and brain by Crone in 1965. It occurs by stereoscopic carrier transport or facilitated diffusion.

There are two mechanisms for the entry of glucose into the CSF from plasma.

1.Carrier mediated diffusion via glucose transporter proteins (GLUT-3 and GLUT-1)[54]

2. Simple diffusion

The former is quantitatively more important, i.e., rate of facilitated diffusion is many times faster than that of simple diffusion at normal blood levels.

There are two mechanisms for the removal of glucose from the CSF.

i. Glucose utilization by various cellular elements (arachnoid, ependymal,neuronal and glial) close to the CSF.
ii. Bulk flow of CSF into the venous system (It's a minor factor).

Diagnostic Significance:

Increased level of CSF glucose is seen in:-

a) Hyperglycemia
b) Premature infants - Relative increase
c) Newborns - Relative increase

Decreased level of CSF glucose is seen in:-

a) Hypoglycemia
b) Meningitis of various etiologies
c) Meningeal neoplasms and meningeal sarcoidosis
d) Neurosyphilis
e) Lupus myelopathy
f) Sub-arachnoid haemorrhage

Mechanism of decreased glucose levels in meningitis:-

Two factors play the key role in decreased CSF glucose in meningitis.

1.The rate of glucose entry:- Experimental studies have shown that damage to the membrane transport mechanism is the cause for inhibition of glucose transport. In meningitis, it may be due to the fact that the membrane carrier is altered by metabolic products of pathological cells that infiltrate the meninges.

2. The rate of glucose utilization:- The reduction in CSF glucose level in meningitis has been found to reflect in part, increased glycolysis by polymorphonuclear leukocytes particularly when these cells are in a state of active phagocytosis, as well as increased glycolysis by the brain cells. The increase in granulocytes in CSF in meningitis and also presence of bacteria which utilize glucose may also account for the decreased glucose level in the CSF.[55]

PROTEINS:

Proteins are the main material of the animal tissues for they constitute approximately 75% of the dry weight.[56] Proteins occupy a central position in the architecture and functioning of living matter. They are intimately connected with all phases of chemical and physical activity that constitute the life of a cell.

The CSF Protein:

Almost all the proteins normally present in CSF are derived from the serum, with the exceptions of the β and γ trace proteins, tau protein, myelin basic protein and glial fibrillary acidic proteins which appear to originate within the brain (i.e. by intrathecal synthesis). Protein concentration gradient along the neuraxis:

In normal infants and adults, there is a concentration gradient of protein from a low level in ventricles (6-15 mg/dl) to an intermediate level in cisterna magna (15-25mg/dl) to the highest level in lumbar sac (20-50 mg/dl).

This finding was explained on the basis of relatively increased permeability of blood-CSF barrier to proteins in the spinal subarachnoid space.

Normal CSF protein under lumbar puncture is 15-45 mg/dl.

Protein size and CSF composition:

An extensive literature supports the generality that the CSF protein composition is related inversely to the molecular weight of the serum proteins. Exceptions to this rule include transferrin and transthyretin which are synthesized in CSF itself by the choroid plexus.

Mechanism of protein entry into CSF:

The current views of protein entering into the CSF from serum through the bloodbrainbarrier, is that it depends on pinocytosis across the capillary endothelial cells of the brain and spinal cord. It is also observed that the rate of protein entry depends upon its isoelectric point and this rate is decreased by acetazolamide which signifies, that the normal protein exchange involves more than restricted filtration.

Protein exit from CSF:

CSF proteins normally leave the CSF by passage across arachnoid villi into venous blood presumably by macrovesicular transport i.e., multiple vesicles are present in the arachnoid villi which provide the mechanism for bulk reabsorption of fluid and passage of proteins.

CSF proteins may be increased in the following conditions:

1. Inflammation due to the increased permeability of blood brain barrier.
2. Abscess, spinal tumor and prolapsed intervertebral disc above the point of sampling; causing partial or complete block leading to the reduced flow of spinal CSF.
3. Humoral immune response within CNS resulting in the intrathecal synthesis of immunoglobulins.
4. Destructive diseases of CNS due to the increased release of brain cellular proteins into CSF.
5. Defect in protein absorption may contribute to increase in the CSF protein.

Decreased CSF protein is seen in:

1. Normal young children between 6 months – 2 years.
2. When large volumes of CSF is removed as in lumbar puncture (LP)
3. When CSF extradural leak occur following LP.
4. In patients with acute water intoxication and in leukemic patients.[57]

CSF protein in meningitis:

The probable mechanism for increased protein in pyogenic meningitis is due to the defect in protein absorption along with increased permeability of the blood-CSF barrier. This mechanism holds true for the increased CSF proteins in tubercular

meningitis and viral meningitis as well. However, the increase in CSF protein levels in tubercular meningitis is less when compared to the levels in pyogenic meningitis.

In 1979, Dermot Kennedy and co-workers studied tubercular meningitis in detail. They found that CSF protein levels were significantly raised in two-thirds of the cases and hypoglycorrhachia was characteristic. They also observed that the prognosis was influenced by both age of the patient and duration of the illness.[58]

In 1985 Ramesh Prasad and co-workers studied meningococcal meningitis in detail. They established that a) the mode of onset was rapid with fever being the commonest presenting feature, b) CSF sugar was very low in more than half of the cases, while in 25% of cases it was marginally low and c) CSF proteins were high in two-thirds of the cases, while normal in 12.5% of cases. In all these cases CSF was turbid and under increased tension.[59]

In the same year, Natalie C. Klein and co-workers studied the clinical course of tubercular meningitis. They observed that fever, lethargy and headache were the commonest symptoms. In majority of cases CSF proteins were higher than normal and in50% of cases CSF glucose was below average. Hypoglycorrhachia was characteristic and hydrocephalus the most common complication. They also noticed older age, presence of underlying disease and inadequate treatment as the poor prognostic factors.[60]

In 1989, B Vishnu Bhat and co-workers studied pyogenic meningitis in detail. They observed that high fever was the commonest presenting feature, CSF glucose was less than normal in 75.8% of cases, CSF protein was above the average in 87.5% of cases and Diplococcus pneumoniae was the commonest cultured organism. They concluded that absence of neck stiffness, normal CSF cell count, sugar, protein and absence of turbidity do not rule out meningitis.[61]

In 1993, Marlene Durand and co-workers studied acute bacterial meningitis in adults. They observed that half of the patients had hypoglycorrhachia, and 96% had elevated protein levels. Ten percent of the patients had an absence of nuchal rigidity, late onset of seizures and highly abnormal CSF findings.[62]

In the same year, V. Gupta studied bacterial meningitis in detail. He observed that CSF was turbid with protein significantly high, and showing hypoglycorrhachia. He also observed that severely depressed CSF sugar and high initial protein might be associated with hearing impairment as a complication in children.[63]

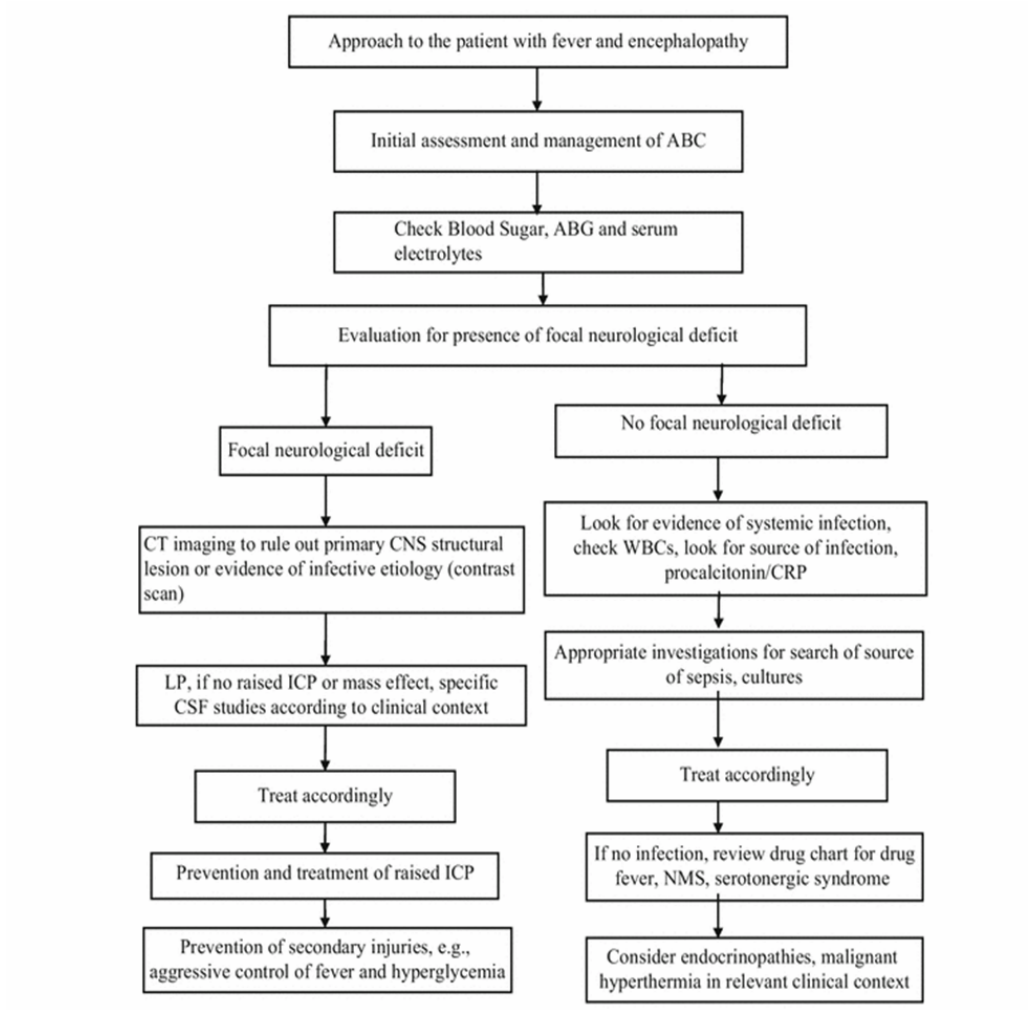
In 1997, Bryndis Sigurdardottir and co-workers studied acute bacterial meningitis in adults. They observed that N. meningitis affected mostly younger age group and S.pneumoniae affected the older age group. CSF analysis showed decreased glucose and increased total protein levels in nearly all the patients. Mortality in meningococcemia was16% and that in pneumococcal disease was 26%. They also found that 1 in 5 adultpatients.[64]

In 1998, Hosoglu and co-workers studied tubercular meningitis in adults. They observed headache as the commonest symptom, CSF sugar was very much reduced and CSF protein significantly high, CSF/blood glucose ratio being 27%. Factors predicting fatal outcome were low glucose, low CSF/ blood glucose ratio, and high CSF proteinlevels.[65]

In 1999, Sormunen and co-workers studied gram negative bacterial meningitis with viral meningitis. They noticed enormously high CSF protein levels and reduced glucose levels in patients with bacterial meningitis.[66]

In the same year, Kelly JJ and co-workers studied in detail the diagnosis and treatment of complicated tubercular meningitis. They established that CSF glucose was typically reduced and protein levels were significantly high.[67]

Acute febrile encephalopathy management:



MATERIALS AND METHODS

- **STUDY GROUP :**

All Patients who are admitted to RLJH medical ICU with complaints of fever with altered sensorium and/or loss of consciousness.

- **STUDY DURATION** :

FEBRUARY 2013 – MARCH 2014

- **METHODS :**

Inclusion Criteria:

1. All patients aged above 18years who present with fever of less than 15 days duration with altered mentation (measured by using Glasgow coma scale, GCS <9/15) either at onset or following fever, and lasting at least 24 hrs. Informed consent will be taken from the spouse or relatives

Exclusion Criteria:

1. Patients with metabolic derangement as the primary cause for persistent alteration in mentation.
2. Patients having cerebrovascular accident followed by fever will also be excluded.
3. History of substance abuse will be excluded.

Method of collection of data:

- All Patients demographic data including name, age, occupation, address will be collected.
- Detailed history of symptom duration, onset and progression will be taken from patient's reliable attendant.
- Clinical examination of heart rate, blood pressure, and especially neurological examination for signs of meningial irritation, cranial nerves involvement, motor and sensory system examination to name a few will be done on all patients.
- All required Laboratory investigations including CSF analysis and blood culture will be done.
- Neuroimaging studies (CT/MRI) will be done.

INVESTIGATIONS

1. **CBC.**
2. **Chest x ray**
3. **Serology including dengue and leptospira if suspected**
4. **Lumbar puncture for CSF analysis**
5. **Blood culture**
6. **Blood smears for malarial parasite**
7. **CT/MRI Brain.**
8. **EEG if required.**

DIAGNOSTIC CRITERIA

- **PYOGENIC MENINGITIS** : Fever with Altered sensorium (without focal symptoms/signs)+/- neck signs + CSF cytology (predominantly polymorphs) + meningeal enhancement on either CT or MRI brain.

- **VIRAL ENCEPHALITIS** : Fever with Altered sensorium (with focal symptoms/signs))+/- neck signs + CSF cytology (predominantly Lymphocytes) + EEG/CT/MRI evidence of parenchymal disease + CSF serology (if available)

- **TUBERCULAR MENINGITIS** : Fever with Altered sensorium (with or without focal symptoms/signs)+/- neck signs + CSF cytology (predominantly Lymphocytes with increased protein and decreased glucose) + CT/MRI finding.

- **CEREBRAL MALARIA** : Fever with Altered sensorium (without focal symptoms/signs) + Peripheral smear/HRP antigen test positive for malaria.

Statistical Analysis:

Data was entered into Microsoft excel and analyzed using EPI info 7 version software. Data was represented in the form of Frequencies and Percentages. Bar diagrams and Pie charts were used for graphical representation of the data. Chi-square test was the test of significance for qualitative data and ANOVA was the test of significance for Quantitative data when more than 2 groups was there. p value <0%5 was considered statistically significant.

RESULTS

In the present study 100 subjects presenting with febrile encephalopathy were included during the study period.

Table 3: Age distribution of the Subjects

Age Group	Frequency	Percent
<30	17	17%
31 to 40	40	40%
41 to 50	12	12%
>50	31	31%
Total	**100**	**100%**

The mean age among the subjects was 42.79 ± 13.19. Majority of the subjects i.e. 40% were in the age group of 31 to 40 yrs, followed by 31% in age group >50yrs.

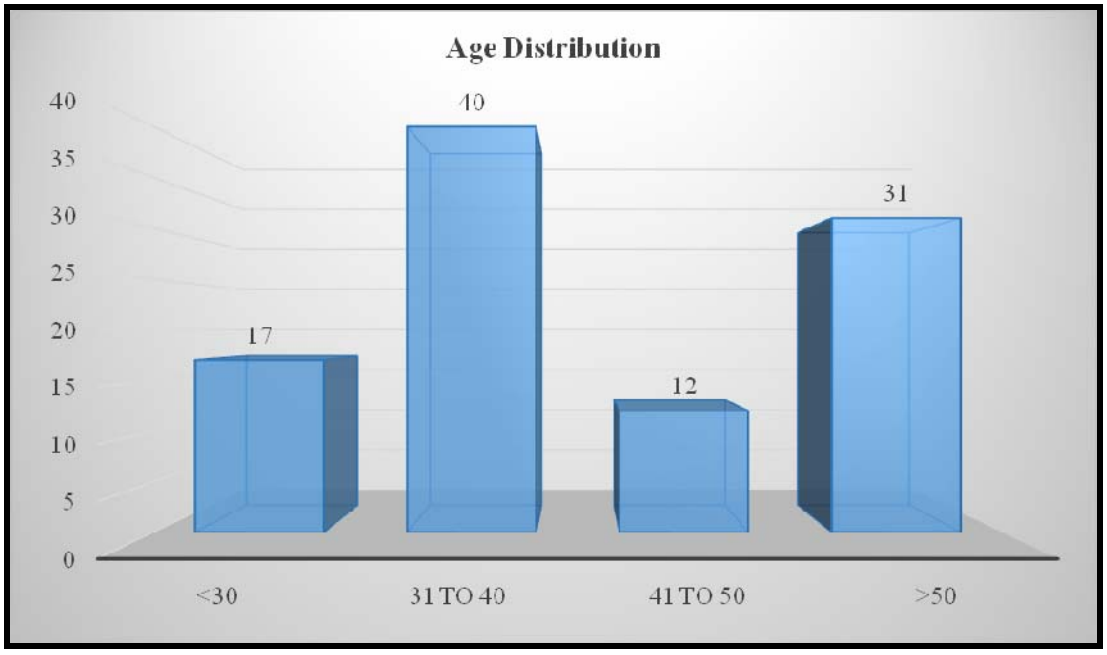


Figure 6: Age Distribution of the subjects

Table 4: Sex Distribution of Subjects

Sex	Frequency	Percent
Female	21	21%
Male	79	79%
Total	**100**	**100%**

In the study it was observed that majority I.e. 79% of subjects were Males and 21% were females.

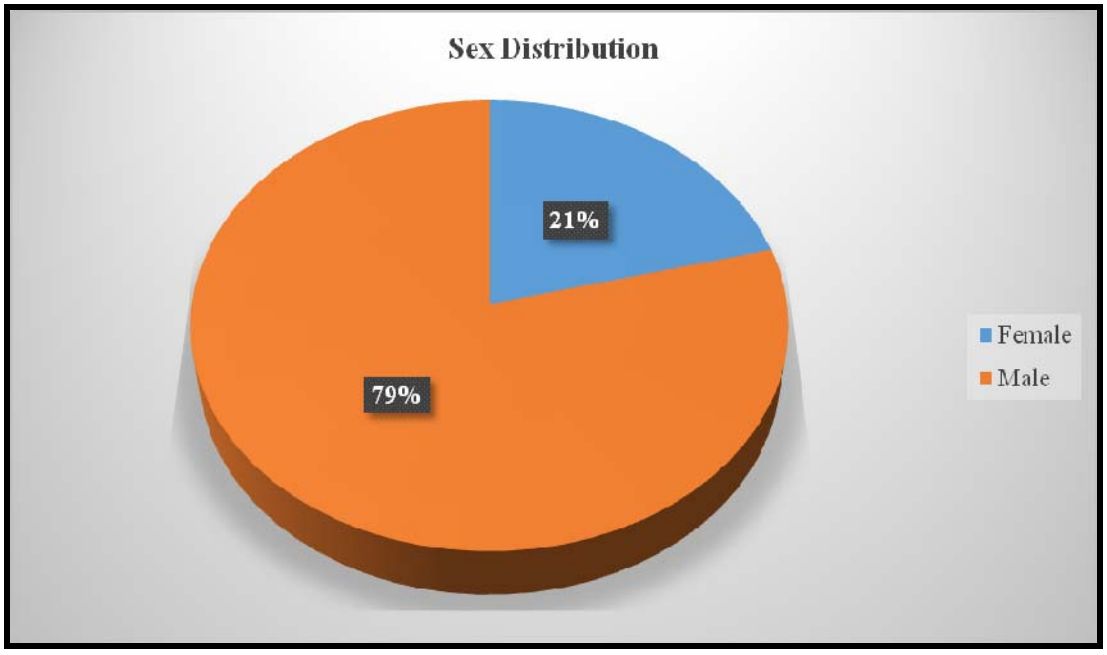


Figure 7: Pie Diagram showing Sex Distribution of the subjects

Table 5: Characteristics of Fever among the subjects

		Frequency	Percent
Fever	**<7days**	28	28%
	>7days	72	72%
Type of Fever	**High grade**	16	16%
	Low grade	84	84%
Associated Feature	**Chills**	21	21%
	No chills	79	79%

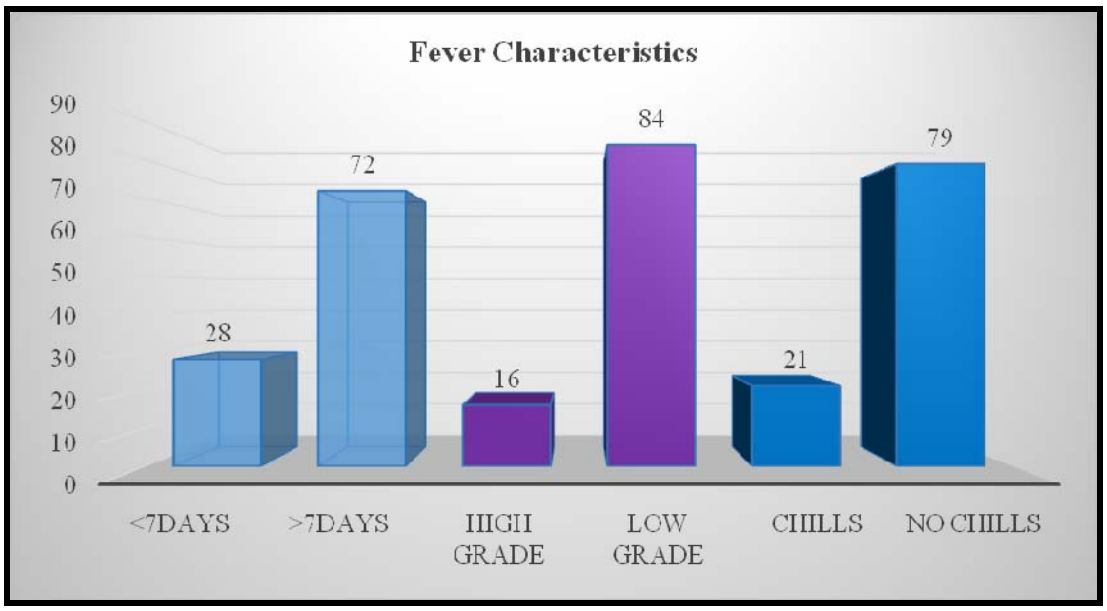


Figure 8: Bar diagram showing Characteristics of Fever

In the study it was observed that majority i.e. 72% of the subjects had fever for more than 7 days and 28% had fever <7days. Mean duration of fever among the subjects was 9.45 ± 2.823 days

In the study majority i.e. 84% of subjects had low grade of fever and 16% had high grade of fever. In the study 79% had no associated feature with fever, 21% had chills.

Table 6: Clinical Presentation of the subjects

Clinical Presentation		Frequency	Percent
Altered sensorium	**<24 hrs**	31	31%
	>24 hrs	69	69%
Headache	**No**	60	60%
	Yes	40	40%
Projectile Vomiting	**No**	84	84%
	Yes	16	16%
Seizures	**No**	67	67%
	Yes	33	33%
Neck Stiffness	**No**	70	70%
	Yes	30	30%
Cranial Nerve Involvement	**No**	82	82%
	Yes	18	18%

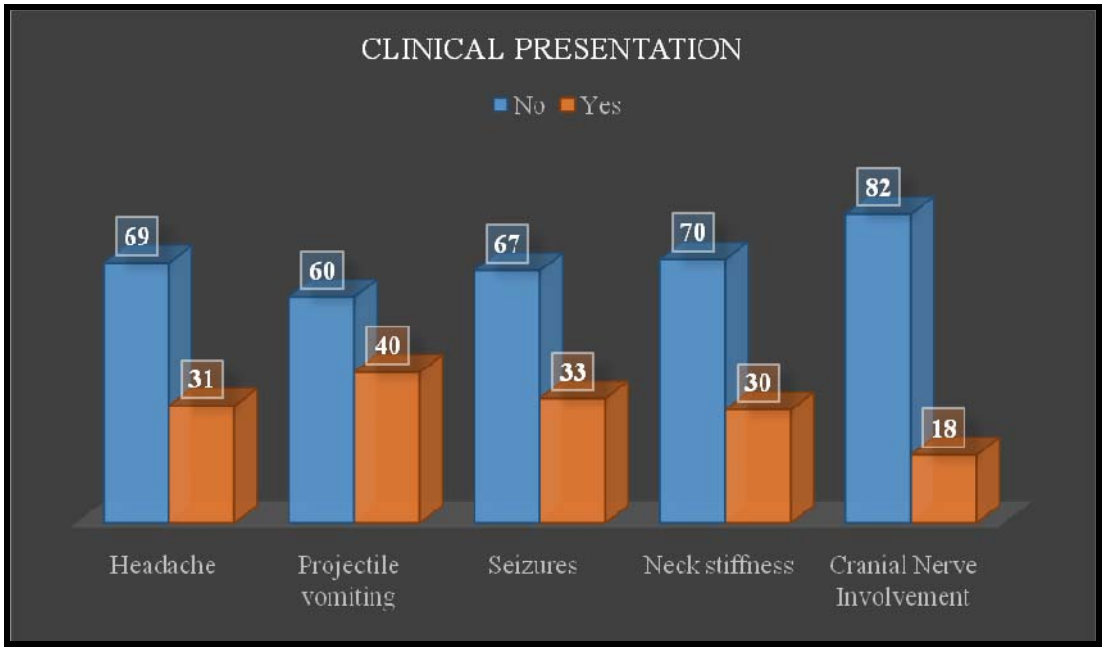


Figure 9: Bar diagram showing clinical presentation of the subjects

The mean duration of altered sensorium among the subjects was 32.69 ± 9.83 days.

In the study 60% of subjects had altered sensorium for <60 days and 40% had altered sensorium for >30 days.

In the study 40% of subjects had headache and 60% did not have headache.

Among the patients with headache majority i.e. 19 had for 4 days, 12 had for 5 days.

Among the subjects only 16% had vomiting, it was projectile in nature.

In the study 33% had Seizures which was GCTS in nature, 67% did not have seizures in the entire course of stay.

In the study it was observed that only 30% presented with neck stiffness and 70% did not have neck stiffness.

In the study 18% had cranial nerve involvement.

Table 7: Distribution of Subjects according to GCS score

GCS score	Frequency	Percent
4	37	37%
5	23	23%
6	22	22%
7	18	18%
Total	**100**	**100%**

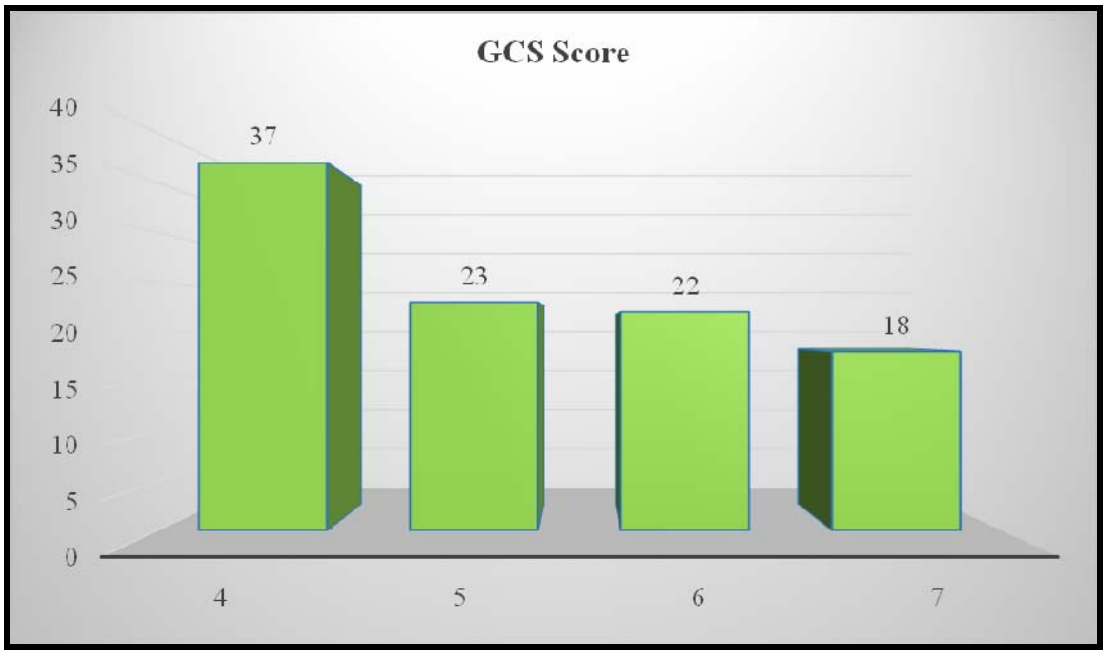


Figure 10: Bar diagram showing GCS score of subjects

In the study 37% had GCS of 4, 23% had GCS of 5, 22% had GCS of 6 and 18% had GCS of 18%.

Table 8: Peripheral smear for Malarial Parasite among 26 subjects of cerebral malaria

Malarial Parasite	Frequency	Percent
Absent	12	46.2%
Present	14	53.8%
Total	**26**	**100%**

In the study 53.8% of subjects were positive for malarial parasite in peripheral smear.

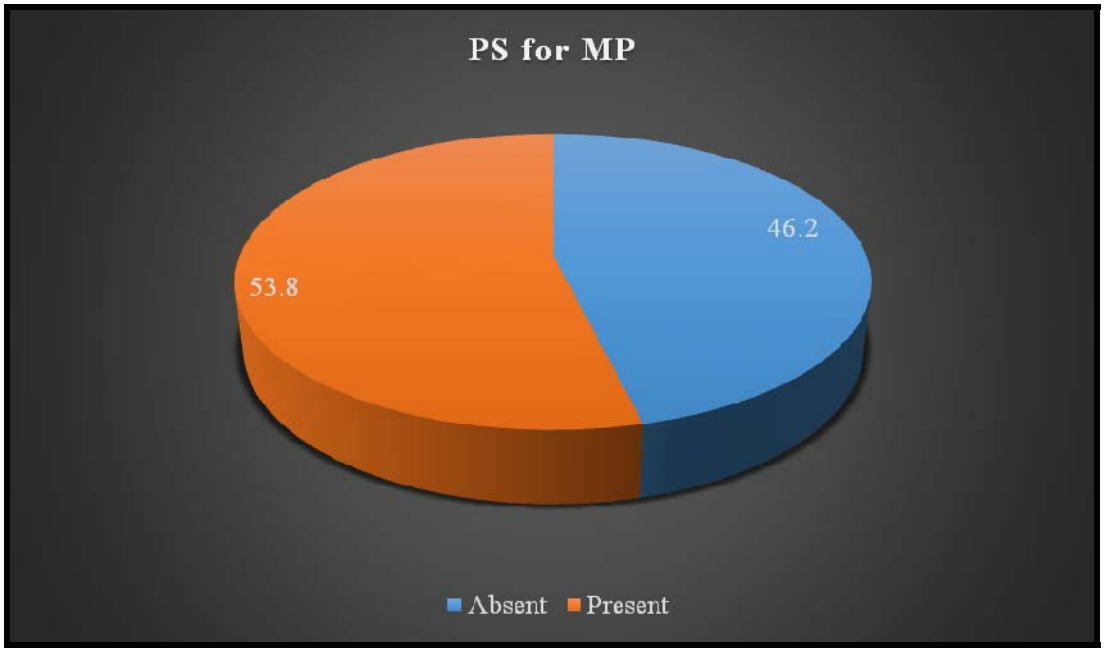


Figure 11: Pie diagram showing peripheral smear findings

Table 9: Viral Serology Findings among the 18 subjects viral encephalitis

Serology Findings	Frequency	Percent
HSV(3)	03	16.6%
JE Virus	01	5.6%
Etiology not confirmative	14	77.7%
Total	**18**	**100%**

In the study it was observed that 16.6% of subjects were positive for HSV 3 virus and 5.6% for JE virus.

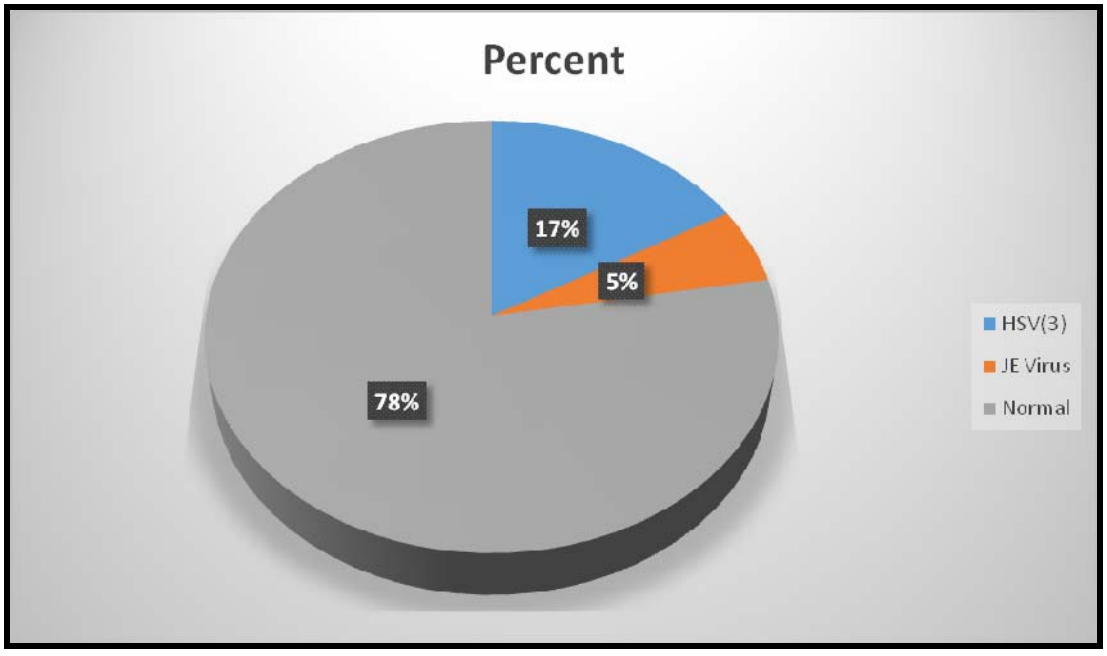


Figure 12: Pie Diagram showing Serology Findings

Table 10: EEG changes among the subjects

EEG	Frequency	Percent
Normal	68	68%
Present	32	32%
Total	**100**	**100%**

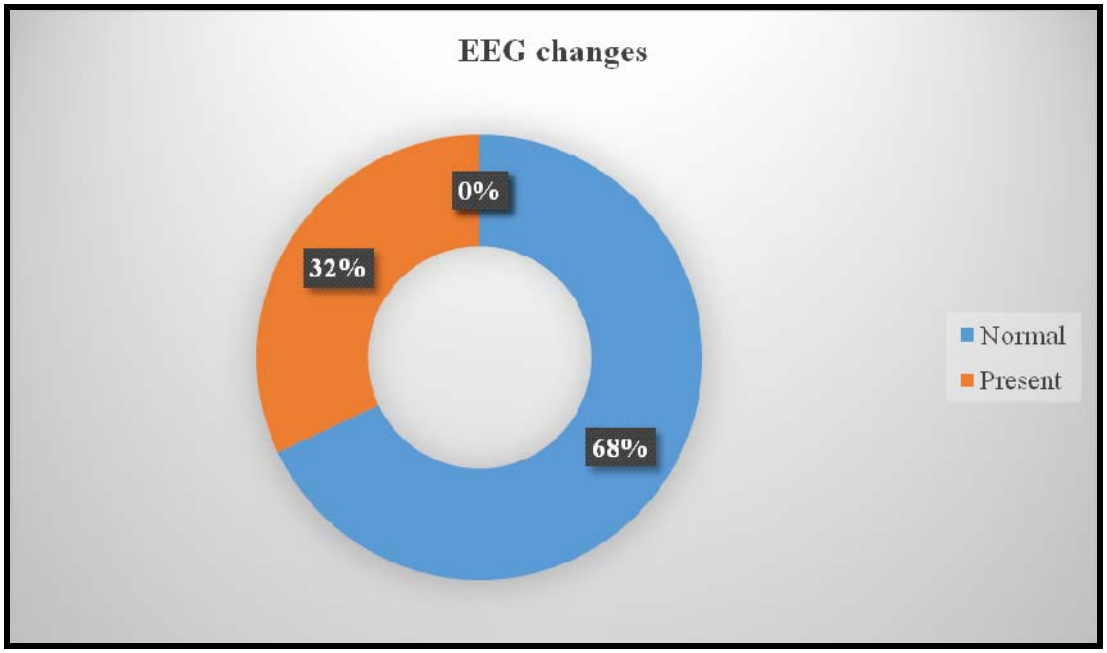


Figure 13: Pie diagram showing EEG changes among the subjects

In the study 32% of subjects had EEG changes.

Table 11: CT/MRI findings of the study subjects

CT/MRI Features	Frequency	Percent
Tuberculoma	21	21%
Normal	46	46%
Encephalitis	18	18%
Meningitis	15	15%
Total	**100**	**100%**

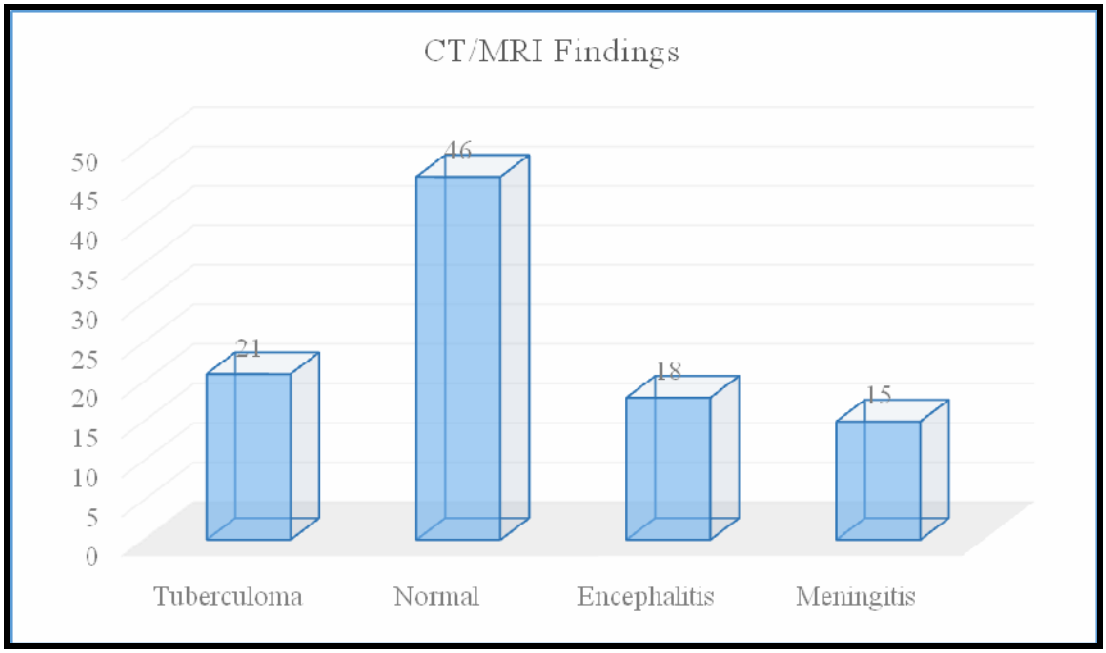


Figure 14: Bar diagram showing different diagnosis

CT/MRI findings in the study showed that 21% had features of Tuberculoma, 18% had Encephalitis features and 15% had Meningitis features.

Table 12: CSF finding among the subjects

Meningitis	Frequency	Percent
TB	41	41%
Malaria	26	26%
Viral	18	18%
Pyogenic	15	15%
Total	**100**	**100%**

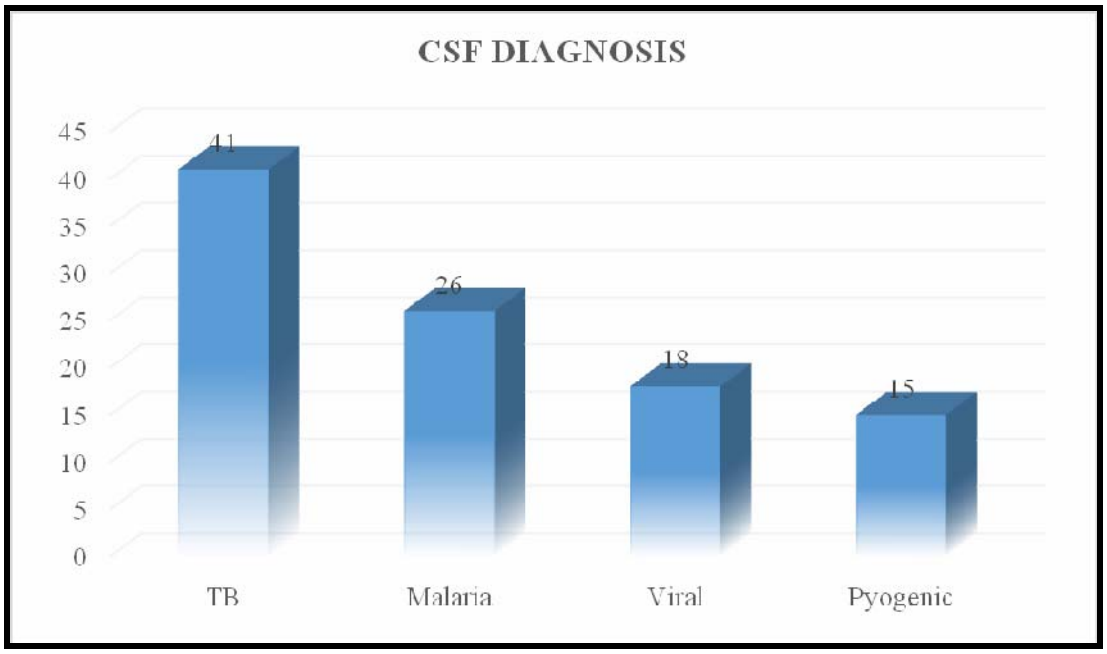


Figure 15: Bar diagram showing CSF findings

CSF analysis among the subjects with febrile encephalopathy showed that majority 41% was due to TB, 26% as malaria, 18% was viral in nature and 15% was pyogenic etiology.

Out of 41 TBM cases only 21 showed features of Tuberculoma in CT/MRI.

Table 13: CSF analysis among the subjects

CSF findings	Cell Count **Mean** ± SD	Protein **Mean** ± SD	Glucose **Mean** ± SD	Chloride **Mean** ± SD
TB (n=41)	368.5 ± 116.2	143.98 ± 5.4	14.46 ± 2.4	125.07 ± 3.9
Malaria (n=26)	5.12 ± 7.8	38.81 ± 7.9	46.31 ± 3.6	116.65 ± 3.7
Viral (n=18)	4.0 ± 1.13	64.33 ± 2.7	45.11 ± 2.7	125.06 ± 3.2
Pyogenic (n=15)	74.07 ± 3.17	86.53 ± 2.92	24.47 ± 2.16	118 ± 2.9

CSF analysis among the subjects showed that Cell count was highest in TB (368.5 ± 116.2), followed by 74.07 ± 3.17 in Pyogenic group. The cell count was least among the Viral etiology i.e. 4.0 ± 1.13.

Similarly Protein was highest in TB (143.98 ± 5.4), followed by 86.53 ± 2.92 in Pyogenic group. Protein was least among the Malaria group i.e. 38.81 ± 7.9.

Glucose levels in CSF was highest in Malaria (46.31 ± 3.6) and Viral group (45.11 ± 2.7). It was least in TB group (14.46 ± 2.4).

Chloride levels was high in TB and Viral group compared to Malaria and Pyogenic group.

Table 14: ANOVA test to compare the mean levels in different diagnostic groups.

ANOVA (Analysis of Variance)		Sum of Squares	df	Mean Square	F	Sig.
Cell count	Between Groups	2953300.919	3	984433.640	174.440	0.001**
	Within Groups	541765.831	96	5643.394		
	Total	3495066.750	99			
Protein	Between Groups	198269.013	3	66089.671	2100.344	0.001**
	Within Groups	3020.747	96	31.466		
	Total	201289.760	99			
Glucose	Between Groups	21374.995	3	7124.998	908%71	0.001**
	Within Groups	753.245	96	7.846		
	Total	22128.240	99			
Chloride	Between Groups	1439.297	3	479.766	36.250	0.001**
	Within Groups	1270.543	96	13.235		
	Total	**2709.840**	**99**			

ANOVA (Analysis of Variance) showed that there was significant difference between mean levels of Cell count, Protein, Glucose and Chloride among TB, Malaria, Viral and Pyogenic group.

Table 15: Predominant Cell type in CSF analysis among different diagnostic groups

		Cell predominant			Total
		Lymphocytes	Neutrophil	Occasional neutrophil	
Meningitis	Malaria	0	0	26	26
	Pyogenic	0	15	0	15
	TB	41	0	0	41
	Viral	16	2	0	18
Total		**57**	**17**	**26**	**100**

$X^2 = 186.42$, df = 6, p = 0.001**

In the study it was observed that there was significant difference in cell count between different diagnoses. In TB predominant cell type was Lymphocytes, in pyogenic cases neutrophil was the predominant cell type. In viral cases lymphocytes was the predominant cell and in malaria occasional neutrophil was the predominant cell. This difference was statistically significant.

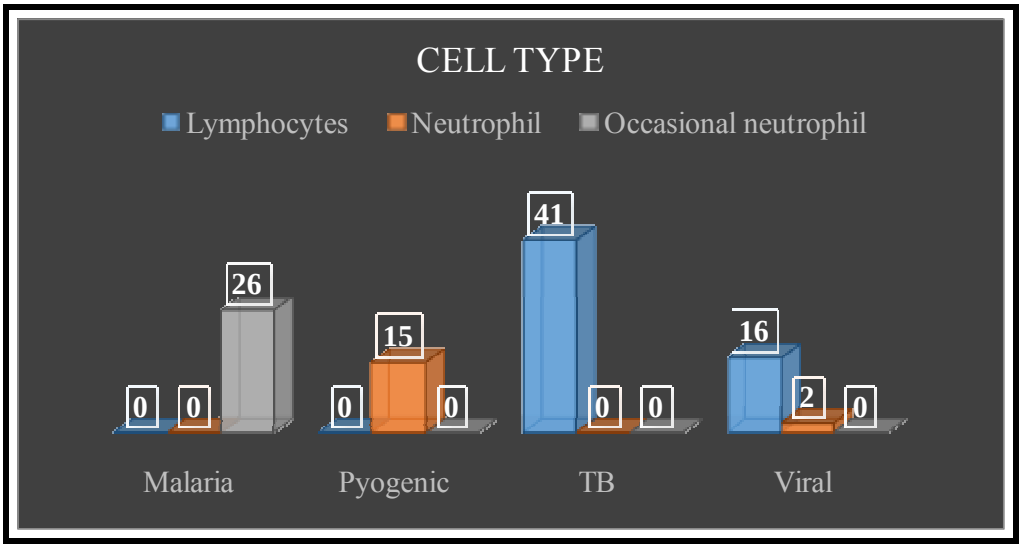


Figure 16: Bar diagram showing Cell type in CSF among different diagnoses

Table 16: Outcome among the subjects presented with febrile encephalopathy after treatment

Outcome	Frequency	Percent
Death	17	17%
Recovered	83	83%
Total	**100**	**100%**

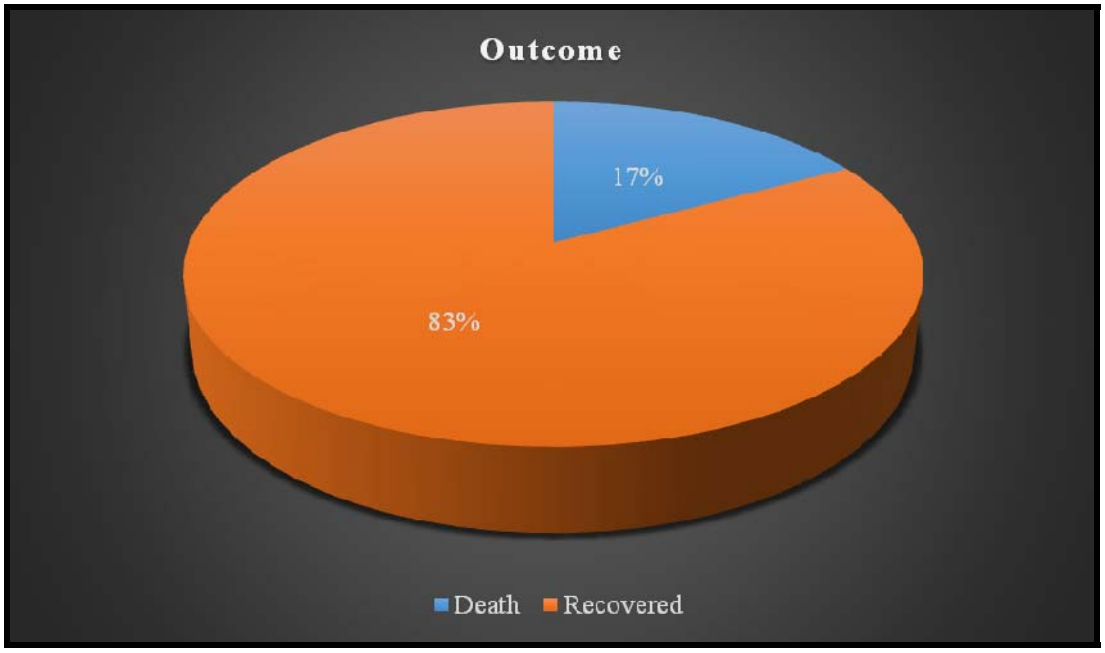


Figure 17: Pie diagram showing the outcome among the subjects presented with febrile encephalopathy

Among the 100 patients studied 17% had mortality and 83% recovered following treatment and discharged later.

Table 17: Outcome among different diagnosis

		Outcome				Total
		Death	Percentage	Recovered	Percentage	
Meningitis	Malaria	2	7.6%	24	92.4%	26
	Pyogenic	6	40%	9	60%	15
	TB	5	12.1%	36	87.9%	41
	Viral	4	22.2%	14	77.8%	18
Total		17		83		100

$X^2 = 8.239$, df = 3, p = 0.041*

In the study it was observed that 40% of pyogenic, 22.2% of viral, 12.1% of TB and 7.6% of Malaria cases had mortality. There was significant association between outcome and diagnosis.

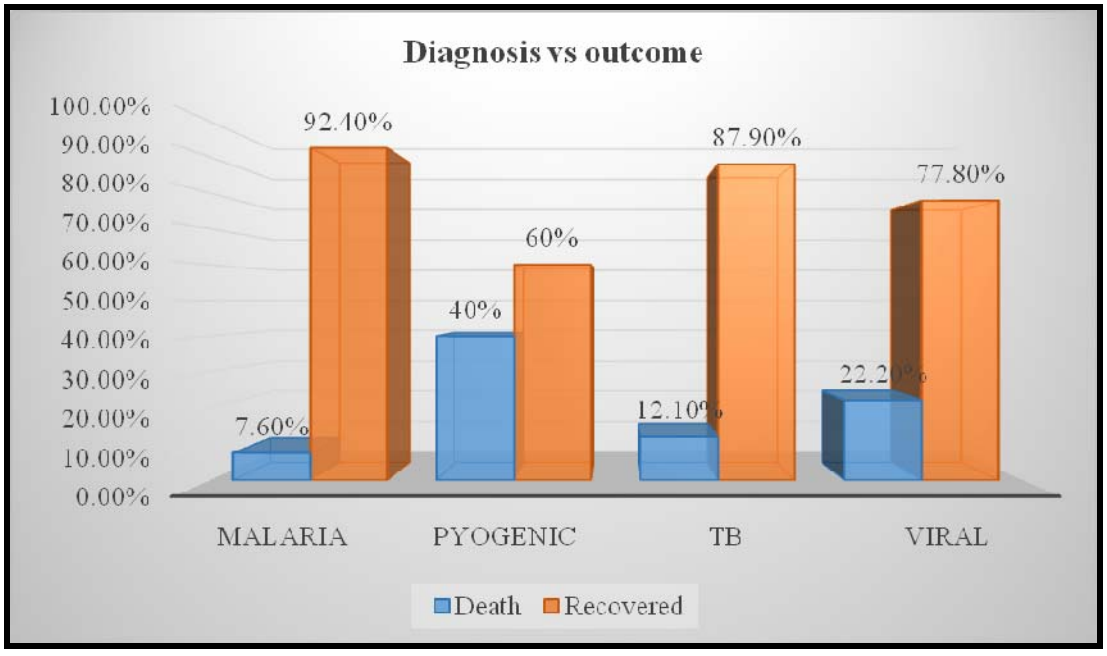


Figure 18: Bar diagram showing Outcome among different diagnosis

Table 18: Mean duration of Hospital stay among the subjects

	No of Subjects	Mean	SD
TB	41	12.39	2.94
Malaria	26	7.38	3.08
Viral	18	28.67	8.52
Pyogenic	15	14.00	3.62

ANOVA					
	Sum of Squares	**df**	**Mean Square**	**F**	**p value**
Between Groups	5109.330	3	1703.110	81.508	0.0001**
Within Groups	2005.910	96	20.895		
Total	**7115.240**	**99**			

In the study it was observed that duration of hospital stay was highest in viral encephalopathy i.e 28.67 ± 8.52 days, least duration was observed in malaria cases i.e. 7.38 ± 3.08.

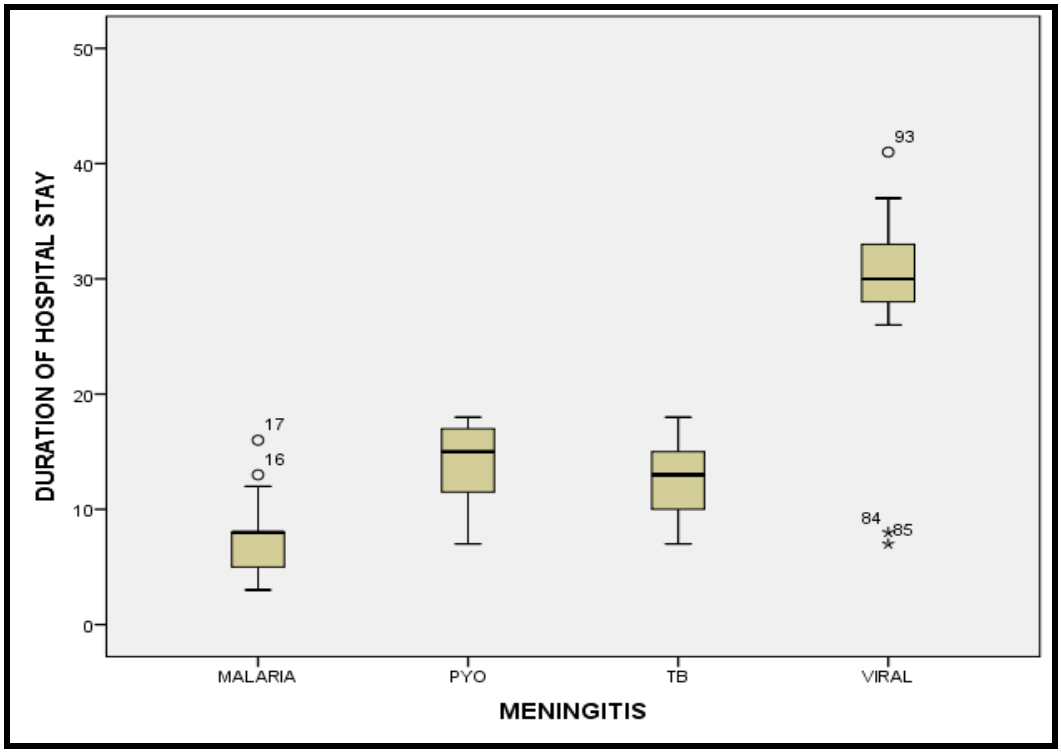


Figure 19: Box plot showing duration of hospital stay

Table 19: Association between age and diagnosis

		Age in Yrs				Total
		<30	31 to 40	41 to 50	>50	
Meningitis	Malaria	6	17	2	1	26
	Pyogenic	0	13	2	0	15
	TB	2	1	8	30	41
	Viral	9	9	0	0	18
Total		17	40	12	31	100

$X^2 = 89.9$, df = 9, p = 0.0001*

In the study it was observed that majority of cases i.e. presented in the 31 to 40 yrs age group, of these 17 were malaria, 13 were Pyogenic and 9 were viral meningitis. Were as after 50 yrs majority i.e. 30 cases were due to TB. There was statistically significant association.

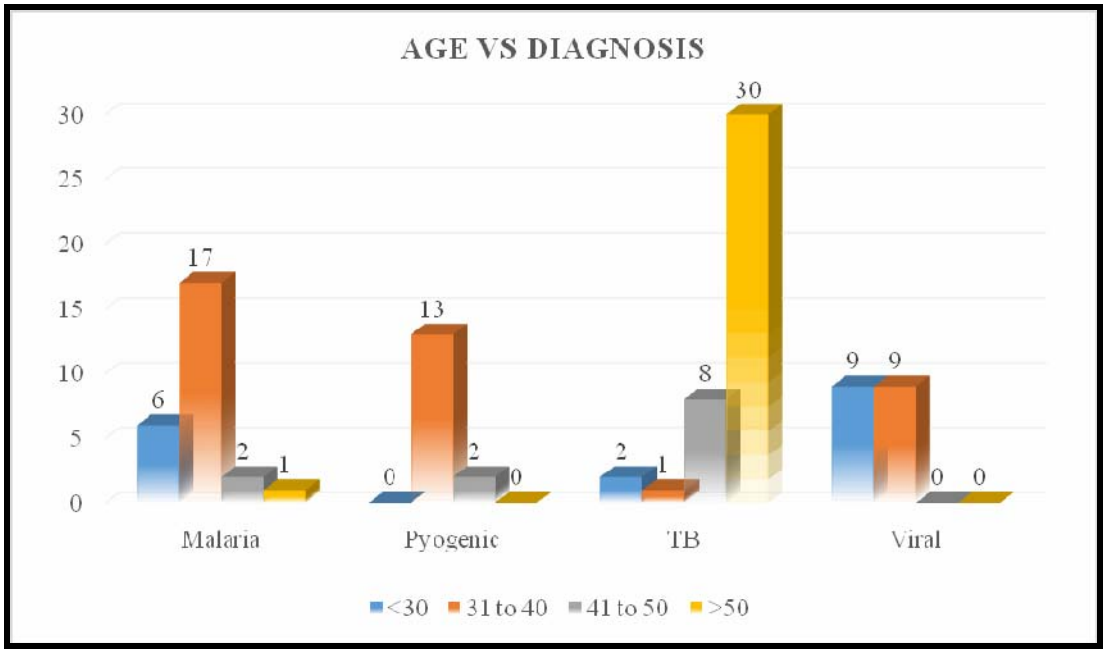


Figure 20: Bar diagram showing association between age and diagnosis

Table 20: Association between diagnosis and sex.

		Sex		Total
		Female	Male	
Meningitis	Malaria	4	22	26
	Pyogenic	4	11	15
	TB	10	31	41
	Viral	3	15	18
Total		21	79	100

$X^2 = 1.27$, df = 3, p = 0.736

In the study it was observed that there was no significant association between sex and diagnosis.

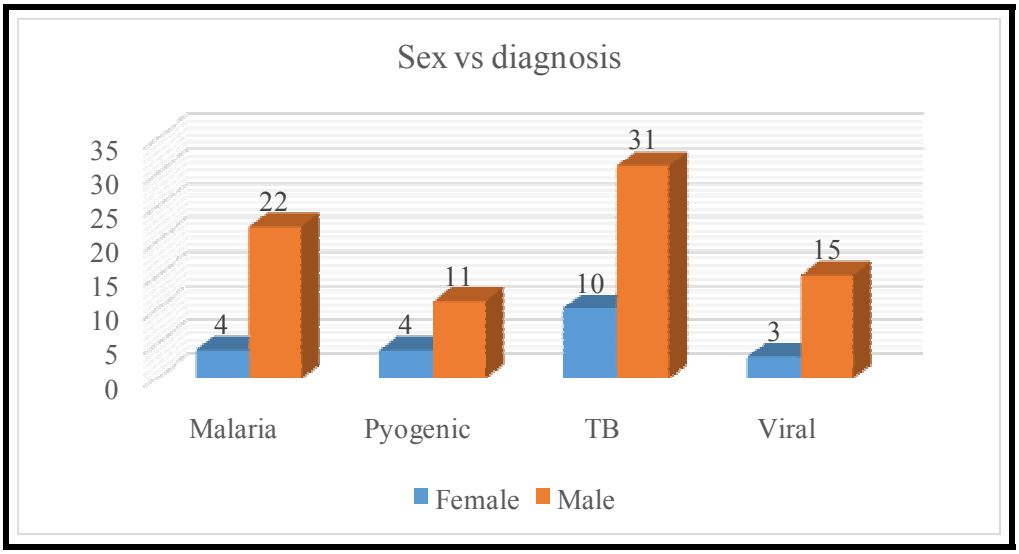


Figure 21: Bar diagram showing association between sex and diagnosis

Table 21: Association between diagnosis and GCS score

		GCS(15)				Total
		4	5	6	7	
Meningitis	**Malaria**	9	6	3	8	26
	Pyogenic	5	3	4	3	15
	TB	15	10	9	7	41
	Viral	8	4	6	0	18
Total		**37**	**23**	**22**	**18**	**100**

$X^2 = 8.605$, df = 9, p = 0.475

In the study it was observed that there was no significant association between diagnosis and GCS score. GCS score was 4 in 37%, 5 in 23% 6 in 22% and 7 in 18%.

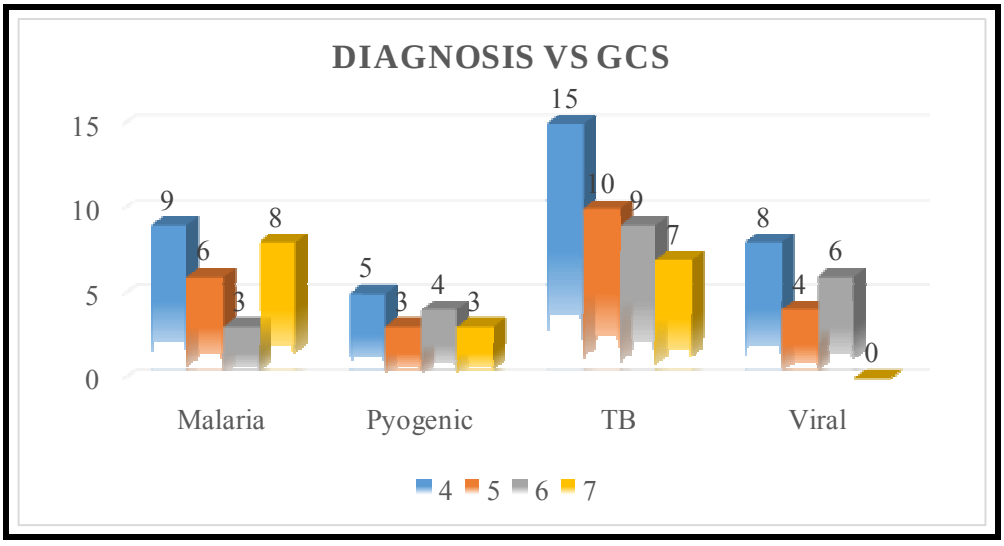


Figure 22: Bar diagram showing Association between Diagnosis and GCS

Table 22: Association between Headache and type of Meningitis

		Meningitis				Total
		Malaria	Pyogenic	TB	Viral	
Headache	Absent	26	15	11	8	60
	Present	0	0	30	10	40
Total		**26**	**15**	**41**	**18**	**100**

$X^2 = 47.945$, df = 3, p = 0.0001**

It was observed that there was significant association between Headache and type of meningitis. Only TB and Viral Meningitis presented with Headache among the study group.

Table 23: Association between Vomiting and type of Meningitis

		Meningitis				Total
		Malaria	Pyogenic	TB	Viral	
Vomiting	Absent	26	15	25	18	84
	Present	0	0	16	0	16
Total		**26**	**15**	**41**	**18**	**100**

$X^2 = 27.41$, df = 3, p = 0.0001** [Does not meet Cochran criteria]

It was observed that there was significant association between vomiting and type of meningitis. All the subjects who presented with projectile vomiting was diagnosed as TB Meningitis.

Table 24:Association between Seizures and type of Meningitis

		Meningitis				Total
		Malaria	Pyogenic	TB	Viral	
Seizures	Absent	15	15	25	12	67
	Present	11	0	16	6	33
Total		**26**	**15**	**41**	**18**	**100**

$X^2 = 9.081$, df = 3, p = 0.028** [Does not meet Cochran criteria]

There was significant association between Seizures and type of meningitis. Malaria, TB and Viral Menigitis presented with seizures. No seizures among the pyogenic group.

Table 25: Association between Neck Stiffness and type of Meningitis

		Meningitis				Total
		Malaria	Pyogenic	TB	Viral	
Neck stiffness	Absent	26	15	11	18	70
	Present	0	0	30	0	30
Total		**26**	**15**	**41**	**18**	**100**

$X^2 = 61.67$, df = 3, p = 0.0001** [Does not meet Cochran criteria]

It was observed that only 30 cases of TB meningitis presented with Neck stiffness. This association was found statistically significant.

Table 26: Association between Cranial Nerve involvement and type of Meningitis

		Meningitis				Total
		Malaria	Pyogenic	TB	Viral	
Cranial Nerve Involvement	Absent	25	15	24	18	82
	Present	1	0	17	0	18
Total		**26**	**15**	**41**	**18**	**100**

$X^2 = 26.06$, df = 3, p = 0.0001** [Does not meet Cochran criteria]

Cranial nerve involvement was more common in TB meningitis, one case in Malaria presented with cranial nerve involvement. This association was found statistically significant.

Table 27: Association between Fever and type of Meningitis

		Meningitis				Total
		Malaria	Pyogenic	TB	Viral	
Character of fever	High	0	15	1	0	16
	Low	26	0	40	18	84
Total		**26**	**15**	**41**	**18**	**100**

$X^2 = 92.74$, df = 3, p = 0.0001** [Does not meet Cochran criteria]

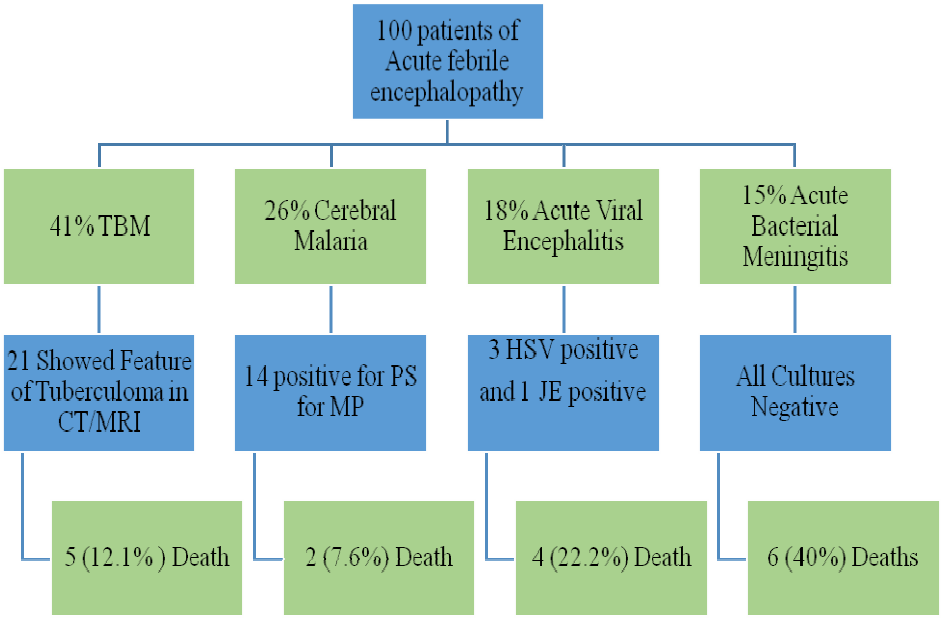
Among majority of the subjects fever was low grade i..e. in 84% and in 16% subjects had high grade of fever of which 15 cases were due to pyogenic meningitis. There was significant association between type of meningitis and character of fever.

Table 28: Association between Chills and type of Meningitis

		Meningitis				Total
		Malaria	Pyogenic	TB	Viral	
Chills	Present	0	0	21	0	21
	Absent	26	15	20	18	53
Total		**26**	**15**	**41**	**18**	**100**

$X^2 = 38.25$, df = 3, p = 0.0001** [Does not meet Cochran criteria]

Fig 23. SCHEME SHOWING THE CAUSES OF ACUTE FEBRILEENCEPHALOPATHY WITH THEIR PROGNOSIS.



DISCUSSION

Fever with altered mentation is a common symptom complexes with large hospital admissions in our country. Fever with altered mental status is commonly produced by bacterial meningitis, Japanese B encephalitis, cerebral malarial, typhoid encephalopathy, and fulminant hepatic failure due to viral hepatitis. Various studies in children with non-traumatic coma have shown that CNS infections are the commonest cause of non-traumatic coma.

A study of non-traumatic coma in children has indicated that tubercular meningitis, pyogenic meningitis (PM), and encephalitis together constitute more than 90% of the cases .[68]

In another study of 151 children, viral encephalitis was the most common etiology seen in 57 patients. A diagnosis other than viral encephalitis was reached in 94 (62.3%) patients. PM was the most frequent diagnosis (33.8%), followed by TBM (7.9%) and CM (5.2%) in the patient group of non-viral etiology.[69]

In our study the results were slightly different, TBM presents in adults as a more sub-acute or chronic form rather than the acute presentation but our study shows high incidence due to lack of health education and irrational use of steroids and poor self care among patients in the rural areas.

In our study, male predominance was seen. This male predominance might be due to the fact that skin amenable to mosquito bites is lesser in women as compared to men in India.

In a study, Panagaria et al. have shown a similar trend of male predominance in HSV encephalitis.[70] Although none of the CNS infections are known to have a male predominance, this apparent male predominance can be attributed to the male dominated social system where a sick male gets preferential medical attention.

The age group of patients which was seen in the study was between18 and 70 years. The mean age among the subjects was 42.79 ± 13.19.(Table 3) Majority of the subjects i.e. 40% were in the age group of 31 to 40 yrs, followed by 31% in age group >50yrs. Similar grouping was found in another study by modi et al. The age of patients was ranged from 13 to 70 years with a mean of 31.89 ± 14.24 years.
In a study by Mohan Kashinkunti et al. The age of patients ranged from 16 to 77 years with a mean of 33.2 ± 12.4 years.

In our study there were 79 (79%)males and 21 (21%) females (table 4). In a study by modi et al there were 76 (63.3%) males and 44 (36.7%) females. In a study byMohan Kashinkunti et al there were 58(58%) males and 42(42%) females.

In our study the most common complaint was fever (100%) (Table 5), altered sensorium (100%) and headache (40%) (table 6). In a study by modi et al. the most common complaints were fever (100%), headache (100%), and altered mental state

(100%). In a study byMohan Kashinkunti et al the most common complaints were fever (100%), headache (92%), and altered mental state (90%).

In our study the Glasgow Coma Scale (GCS) score at the time of presentation was 37% had GCS of 4, 23% had GCS of 5, 22% had GCS of 6 and 18% had GCS of 7 (table 7).The Glasgow Coma Scale (GCS) score at the time of presentation was ≤7 in 21 (17.5%) patients, while 99 (82.5%) patients had a GCS of >7 in a study by modi et al. In a study by Mohan Kashinkunti et al the Glasgow Coma Scale (GCS) score at the time of presentation was ≤7 in all the patients.

In our study 83 (83%) of patients recovered and 17 (17%) died during the hospital stay (table 16). Out of the 17 patients ,4 with Acute Viral Encephalitis, 5 with tubercular meningitis, 6 due to pyogenic meningitis and 2 due to cerebral malaria (table 17) was seen.

An attempt was made to study the patient outcome i.e recovery or death and the type of encephalopathy in our study, it was observed that 40% of pyogenic, 22.2% of viral, 12.1% of TB and 7.6% of Malaria cases had mortality (figure no 18). There was significant association between outcome and diagnosis. In a study conducted by Mohan Kashinkunti et al , similar results were reported. 18 patients died during the hospital stay, 8 with AVE, 5 with sepsis associated encephalopathy, 3 due to pyogenic meningitis and 2 due to cerebral malaria.

In a study at CSMMU at Lucknow, Of the total 120 patients, 16 patients died, 6 with AVE, 3 with pyogenic meningitis, 3 with cerebral malaria, and 4 with SAE.

It is postulated that alteration in sensorium in a patient with CNS infection indicates an element of parenchymal involvement.[69,71] This can explain the altered mental state in patients with meningoencephalitis.

In CM and leptospirosis, primary parenchymal involvement may be responsible for encephalopathy, but altered mentation in primary meningeal involvement is difficult to explain. Raised intracranial pressure may contribute to altered mentation to some extent. The reason for altered sensorium in meningitis is postulated to be the spillage of inflammatory cells to the adjacent brain parenchyma and the resultant parenchymal involvement.[71]

HSV is a common cause of sporadic encephalitis around the world.[72] Post-monsoon JE has been reported from many parts of India. The less common varicella encephalitis tends to be fatal in immunocompromised patients. Among the other identifiable viruses, enterovirus, JE virus, and mumps are the important agents.[69]

In our study, the most commonly identifiable cause of encephalitis was herpes simplex encephalitis in three patients followed by one patient with JE(table 9). The complete virologic screen was not available to us and hence, we could not identify the culprit virus in a substantial number of our patients.

CM, the potentially fatal complication of falciparum malaria is an important cause of unarousable coma in febrile patients in endemic areas. In the endemic areas, CM remains an important differential diagnosis in patients presenting with acute fever and altered mental state.[73]

In our study since kolar is a malaria endemic area, it was the second most common cause for acute febrile encephalopathy (26 out of 100 patients).Post-monsoon surge in malarial cases coincides with that of viral encephalitis and the common symptomatology may be confusing to the treating physician. We have encountered a large number of CM cases in our study group with a post-monsoon surge, which suggests that northwest India is also endemic for malaria, in contrast to the previous studies.[74]

Dengue hemorrhagic fever presents as a short febrile illness and thrombocytopenia, but may rarely present with alteration in sensorium. In a study, 62 of 265 patients with AFE from central India tested positive for dengue serology and only 39 met the criterion for definite dengue virus infection.[75]Although we do see epidemics of dengue virus infection every year, in the present study, we did not categorize patients into a separate dengue encephalopathy group, though not many patients showed positive serology for dengue in serum.

In a Study on Cerebral malaria caused by Plasmodium vivax in adult subjects, I.M.S. Banaras Hindu University, Varanasi ,Uttar Pradesh, India. All the three patients had PS for MP Positive. In our study 53.8% (14 out of 26) of subjects were positive for malarial parasite in peripheral smear.(fig no 11).

The patients were treated with supportive therapy and intravenous Artesunate in the recommended dose. Repeat blood smears after two days of therapy showed clearance of the parasites.

CT scan brain was performed as baseline imaging in all the patients with AFE firstly to rule out contraindications for lumbar puncture. Enhancement of the meninges was seen on contrast-enhanced CT scan in cases of bacterial meningitis. However, meningeal enhancement is a nonspecific sign and may also be caused by other different etiologies like carcinomatous meningitis, reactive meningitis, and inflammatory vascular diseases of CNS. Imaging studies performed in patients with acute meningitis may provide normal findings.

Our results also showed normal CT imaging in most of the patients.(fig no 14) CT/MRI findings in the study showed that 21% had features of Tuberculoma, 18% had Encephalitis features and 15% had Meningitis features and 46% had a normal CT/MRI Brain.

Therefore, the results of an imaging study do not exclude or prove the presence of acute meningitis. MR imaging of brain offers better resolution, it was performed when the findings of CT scan and CSF were inconclusive and patients were not fitting into the criteria of either CM or SAE. MRI brain in patients with HSV encephalitis and JE may have characteristic findings as demonstrated in our patient with JE[76] and HSV encephalitis.[77]

Bilateral T2 thalamic hyperintensities, in particular hemorrhage, was the most common finding seen in patient with JE, in whom MRI brain was done.
MRI brain in all 3 patients with HSV encephalitis showed characteristic T2-weighted hyperintensities in the temporal lobes (table no 9).

Many acutely ill febrile patients with encephalopathy can make complete recovery once the underlying cause is treated, but considerable skill is required to correctly diagnose the underlying etiology. The majority of our patients made a complete recovery; however, a significant number of patients died and a small number of patients were also left with neurologic sequelae. One patient of JE encephalitis was left with poor cognitive impairment. Delayed neurologic recovery and sequelae are well described with meningoencephalitis.[77]

In our study out of 100 patients 41(41 %) patients were diagnosed with tubercular meningitis, 26 (26%) patients with cerebral malaria, 15(15%) patients with pyogenic meningitis and 18 (18%) with acute viral encephalitis. Out of the 18 (Japanese B encephalitis in 5.6%, herpes simplex virus encephalitis in 16.66%, and other undetermined viral etiology in 77.7%) (fig no 12.).

In another study conducted at SDMCMS & H, Dharwad.[78] Out Of the total 100 patients studied, acute viral encephalitis (AVE) was the most common etiology (34%), followed by sepsis associated encephalopathy (SAE) (29%), pyogenic meningitis (PM) (22%). Cerebral malaria (CM) and Tuberculous meningitis (TM) was diagnosed in 6%, and 5% of cases, respectively.

In that study, acute viral encephalitis was the common etiology followed by sepsis associated encephalopathy and pyogenic meningitis.

In another study in by Departments of Medicine and Neurology, CSMMU, Lucknow [79], India, Of the total 120 patients studied, pyogenic meningitis was the most common cause accounting for 36.7%, followed by acute viral encephalitis (AVE) in 28.33% of the patients (Japanese B encephalitis in 12.5%, herpes simplex virus encephalitis in 3.33%, and other undetermined viral etiology in 12.5%). Cerebral malaria, sepsis associated encephalopathy (SAE), and tuberculous meningitis were diagnosed in 21.7%, 9.17%, and 4.2% of cases, respectively.

In a study at Northwestern India by department of Internal Medicine at Postgraduate Institute of Medical Education and Research, Chandigarh, for over a period of 1 year showed that out of 127 patients with AFE, 70% had primary CNS infection as the etiology.

Out of which 33% patients had meningitis, 29.9% had evidence of meningoencephalitis, and 12.7% were diagnosed as sepsis-associated encephalopathy.

In a study at a tertiary referral hospital (Patan Hospital) in Kathmandu, Nepal. Out of 87 patients who were recruited for the study and the etiological diagnosis was established in 38% (n=33).

The bacterial pathogens identified were Neisseria meningitides (n=6); Streptococcus pneumoniae (n=5) and Staphylococcus aureus (n=2) in 13/ 87(14%). Enteroviruses were found in 12/87 (13%); Herpes Simplex virus (HSV) in 2/87(2%).

IgM against Japanese encephalitis virus (JEV) was detected in the CSF of 11/73 (15%) tested samples. But our studies on the culture of CSF in patients with PM did not show any growth.

CONCLUSION

1. In this study Tubercular meningitis is being the most common cause (41%), followed by Cerebral malaria (26%), Viral encephalitis (18%) and Pyogenic meningitis (15%).

2. There is a high incidence of cerebral malaria as it is an endemic area and early detection and treatment helps in improving the outcome of patients.

3. Patients with Pyogenic meningitis had the worst prognosis in terms of survival outcomes.

4. Patients with Cerebral malaria had the best prognosis in terms of survival outcomes.

5. Our study demonstrates that acute febrile encephalopathy in adults is a heterogeneous syndrome with primary CNS infections being the commonest etiology.

SUMMARY

"Acute febrile encephalopathy" is a term commonly used to identify this condition in which altered mental status either accompanies or follows a short febrile illness. It is a common condition leading to hospital admissions in both adults and children in India. Central nervous system (CNS) infections are the most common cause of non-traumatic coma.

Meningitis is the most common form of suppurative central nervous system (CNS) infection which occurs throughout the world. The prognosis of meningitis is critically dependent on a rapid causal diagnosis and implementation of immediate treatment. However, clinical and biochemical parameters available within the few hours that follow patients admission are not reliable enough, except when bacteria are to be found in the cerebrospinal fluid under the microscope. Therefore, the initial treatment of meningitis is most of time presumptive.

The differentiation of acute encephalitis cases from acute encephalopathy is at times quite difficult but certain distinguishing features are worth mentioning.

Presence of low serum glucose, markedly raised liver enzymes, absence of pleocytosis on CSF examination, normal brain scans (except for brain edema), and no residual neurological deficit after recovery are few distinguishing features that should alert a treating clinician to explore a diagnosis other than acute viral encephalitis.

Careful consideration of these finer points of differentiation between the two clinical entities is often necessary to prevent clinicians from pursuing an exhaustive search for a putative virus that never exists.

Acute febrile illness with altered mental status is a common complaint of the patients who have presented to hospital in this part of South Karnataka. An attempt has been made to study the etiology & outcome of acute febrile encephalopathy.

In our study over a period a one year between February2013 to March 2014, a total of 100 patients of acute febrile encephalopathy were studied during this period. Out of 100 patients, 41 (41%) had Tubercular meningitis (TBM), 26 (26%) had Cerebral malaria (CM), 15 (15%) had Pyogenic meningitis (PM) and 18 (18%) had Acute Viral Encephalitis (AVE).

Among the 18 patients with AVE, 3 patients had HSV Encephalitis and 1 patients had JE encephalitis who improved completely with mild cognitive impairment and patients with AVE had poor prognosis in terms of survival outcomes in comparison with the other patients. Out of 26 patients with cerebral malaria, 14 patients had PS for MP Positive and the patients with cerebral malaria had the best prognosis in terms of survival outcomes of the patient.

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ANNEXURE I

PROFORMA

SL No.:

NAME: AGE: SEX:

IP No.:

HISTORY

FEVER: Y / N DURATION (Days):

HEADACHE: Y / N DURATION (Days):

VOMITING: Y / N DURATION (Days):

SEIZURES: Y / N No. OF EPISODES: PARTIAL / GENERALIZED

ALTERED SENSORIUM: Y / N

DROWSY/ IRRITABLE/ STUPOR/COMA:

NEUROLOGICAL DEFICITS: Y / N

ANY OTHER RELEVANT HISTORY:

PHYSICAL EXAMINATION

VITALS:-

BP:

PR:

RR:

TEMP:

OTHERS:

CNS EXAMINATION

HMF:

CRANIAL NERVES:

MOTOR SYSTEM:

PLANTARS:

SENSORY SYSTEM:

CEREBELLAR SIGNS:

NECK STIFFNESS: Y / N

KERNIGS SIGN: Y / N BRUDZINSKI'S SIGN: Y / N

CVS:

RS:

PA:

INVESTIGATIONS

CBC:

Hb %:

TLC:

N= L= M= B= E =

LFT:

RBS:

CXR:

PERIPHERAL SMEAR FOR MALARIAL PARASITE:

SEROLOGY:

CT SCAN BRAIN PLAIN:

MRI BRAIN:

EEG:

BLOOD CULTURE:

HIV TEST:

CSF ANALYSIS:

APPEARANCE:

CELL COUNT:

CELL TYPE: N = L=

MALIGNANT CELLS:

PROTEIN: mg/dl

SUGAR: mg/dl

CHLORIDE:

GRAM STAIN:

AFB STAIN:

ADENOSINE DEAMINASE: U/L

DIAGNOSIS:

TREATMENT:

DURATION OF HOSPITAL STAY:

OUTCOME:

MASTER CHART

SLNO	AGE	Agerecoded	SEX	FEVERDAYS	Feverrecoded	CHARACTER	ASSOCIATEDFEATURE	ALTEREDSENSORIUM	HEADACHE	DURATIONDAYS	VOMITING	CHARACTER_A	SEIZURES	TYPE	NECKSTIFFNESS	CRANIALNERVES	GCS15	PSFORMP	SEROLOGY	Diagnosis	CSFCELLCOUNT	PROTEIN	GLUCOSE	CHLORIDE	CELLPREDOMINANT	CTMRI	EEG	DURATIONOFHOSPITALSTAY	OUTCOME	MENINGITIS	Alteredsensoriumrecoded	ASrecoded
1	40	2	M	8	2	LOW	N	24	N	N	N	N	N	N	N	N	6	Not done	N	4	5	60	45	125	NEUT	ENCEPH	N	30	IMP	VIRAL	1	1
2	28	1	M	6	1	LOW	INTERMIT	25	Y	4	N	N	N	N	N	N	4	Not done	N	4	5	65	45	127	LYM	ENCEPH	N	8	IMP	VIRAL	1	2
3	31	2	M	10	2	LOW	INTERMIT	26	Y	4	N	N	Y	GTCS	N	N	5	Not done	N	4	4	61	46	126	NEUT	ENCEPH	Y	7	IMP	VIRAL	1	2
4	33	2	F	12	2	LOW	N	26	N	N	N	N	Y	GTCS	N	N	4	Not done	N	4	5	68	42	125	LYM	ENCEPH	Y	30	DEATH	VIRAL	1	2
5	27	1	M	8	2	LOW	N	27	Y	4	N	N	N	N	N	N	5	Not done	JE VIRUS	4	3	61	45	123	LYM	ENCEPH	N	37	IMP	VIRAL	1	2
6	38	2	M	11	2	LOW	N	24	N	N	N	N	N	N	N	N	4	Not done	HSV(3)	4	4	67	48	120	LYM	ENCEPH	N	29	IMP	VIRAL	1	1
7	27	1	M	10	2	LOW	N	26	Y	4	N	N	Y	GTCS	N	N	6	Not done	HSV(3)	4	3	66	45	127	LYM	ENCEPH	Y	32	IMP	VIRAL	1	2
8	28	1	M	12	2	LOW	INTERMIT	26	N	N	N	N	Y	GTCS	N	N	4	Not done	HSV(3)	4	4	64	45	124	LYM	ENCEPH	Y	28	IMP	VIRAL	1	2
9	26	1	M	11	2	LOW	INTERMIT	24	N	N	N	N	N	N	N	N	4	Not done	N	4	4	65	42	123	LYM	ENCEPH	N	26	IMP	VIRAL	1	1
10	31	2	M	9	2	LOW	N	27	Y	4	N	N	N	N	N	N	6	Not done	N	4	3	67	45	129	LYM	ENCEPH	N	31	DEATH	VIRAL	1	2
11	36	2	F	6	1	LOW	N	27	Y	4	N	N	N	N	N	N	5	Not done	N	4	5	63	46	126	LYM	ENCEPH	N	41	DEATH	VIRAL	1	2
12	34	2	M	11	2	LOW	INTERMIT	23	Y	5	N	N	Y	GTCS	N	N	6	Not done	N	4	6	66	47	119	LYM	ENCEPH	Y	30	DEATH	VIRAL	1	1
13	30	1	M	5	1	LOW	N	27	N	N	N	N	N	N	N	N	6	Not done	N	4	3	66	42	128	LYM	ENCEPH	N	34	IMP	VIRAL	1	2
14	32	2	M	5	1	LOW	N	27	Y	5	N	N	N	N	N	N	6	Not done	N	4	2	69	50	119	LYM	ENCEPH	N	35	IMP	VIRAL	1	2
15	29	1	M	9	2	LOW	N	25	Y	4	N	N	N	N	N	N	5	Not done	N	4	6	63	50	129	LYM	ENCEPH	N	28	IMP	VIRAL	1	2
16	39	2	M	8	2	LOW	N	23	Y	3	N	N	N	N	N	N	4	Not done	N	4	4	64	45	124	LYM	ENCEPH	N	29	IMP	VIRAL	1	1
17	29	1	F	6	1	LOW	N	26	N	N	N	N	N	N	N	N	4	Not done	N	4	3	60	39	129	LYM	ENCEPH	N	33	IMP	VIRAL	1	2
18	27	1	M	14	2	LOW	N	27	N	N	N	N	Y	GTCS	N	N	4	Not done	N	4	3	63	45	128	LYM	ENCEPH	Y	28	IMP	VIRAL	1	2
19	30	1	M	7	1	HIGH	CHILLS	20	Y	5	Y	PRO	Y	GTCS	Y	Y	7	Not done	Not done	3	150	174	20	120	LYM	NORMAL	Y	10	IMP	TB	1	1
20	56	4	M	6	1	LOW	N	41	Y	4	N	N	N	N	Y	Y	5	Not done	Not done	3	312	148	14	124	LYM	NORMAL	N	14	IMP	TB	2	2
21	61	4	M	7	1	LOW	CHILLS	44	Y	5	N	N	N	N	Y	Y	6	Not done	Not done	3	254	139	17	127	LYM	NORMAL	N	11	IMP	TB	2	2
22	52	4	M	6	1	LOW	N	45	Y	6	Y	PRO	Y	GTCS	Y	Y	6	Not done	Not done	3	413	143	14	124	LYM	NORMAL	Y	13	DEATH	TB	2	2
23	39	2	M	5	1	LOW	CHILLS	41	Y	4	N	N	Y	GTCS	N	Y	5	Not done	Not done	3	346	141	17	125	LYM	NORMAL	Y	15	IMP	TB	2	2
24	29	1	M	13	2	LOW	CHILLS	44	Y	4	N	N	Y	GTCS	Y	N	4	Not done	Not done	3	412	142	14	123	LYM	NORMAL	Y	11	IMP	TB	2	2
25	57	4	M	11	2	LOW	N	43	Y	4	Y	PRO	N	N	N	N	5	Not done	Not done	3	358	145	12	121	LYM	NORMAL	N	10	IMP	TB	2	2
26	42	3	F	9	2	LOW	CHILLS	43	Y	5	Y	PRO	N	N	Y	N	4	Not done	Not done	3	268	141	13	124	LYM	NORMAL	N	14	IMP	TB	2	2
27	63	4	M	9	2	LOW	CHILLS	41	Y	4	Y	PRO	N	N	N	Y	4	Not done	Not done	3	510	143	14	123	LYM	NORMAL	N	7	IMP	TB	2	2
28	58	4	M	12	2	LOW	CHILLS	45	N	N	Y	PRO	Y	GTCS	Y	N	7	Not done	Not done	3	462	141	16	121	LYM	NORMAL	Y	17	IMP	TB	2	2
29	66	4	M	9	2	LOW	CHILLS	46	Y	3	Y	PRO	Y	GTCS	Y	Y	6	Not done	Not done	3	451	146	14	124	LYM	NORMAL	Y	16	IMP	TB	2	2
30	49	3	M	6	1	LOW	N	47	Y	4	N	N	N	N	N	Y	5	Not done	Not done	3	278	144	16	128	LYM	NORMAL	N	10	IMP	TB	2	2
31	54	4	F	13	2	LOW	CHILLS	44	Y	6	N	N	Y	GTCS	Y	N	6	Not done	Not done	3	459	142	14	120	LYM	NORMAL	Y	8	DEATH	TB	2	2
32	71	4	F	11	2	LOW	N	44	Y	6	Y	PRO	N	N	Y	Y	4	Not done	Not done	3	198	141	17	125	LYM	NORMAL	N	18	IMP	TB	2	2

MASTER CHART

33	48	3	M	13	2	LOW	CHILLS	47	Y	5	N	N	Y	GTCS	Y	N	5	Not done	Not done	3	571	145	19	123	LYM	NORMAL	Y	8	IMP	TB	2	2
34	56	4	M	7	1	LOW	CHILLS	45	Y	7	N	N	Y	GTCS	Y	N	4	Not done	Not done	3	367	143	12	127	LYM	NORMAL	Y	13	IMP	TB	2	2
35	51	4	M	8	2	LOW	N	46	Y	4	Y	PRO	N	N	Y	N	5	Not done	Not done	3	467	144	12	130	LYM	NORMAL	N	11	IMP	TB	2	2
36	57	4	F	13	2	LOW	CHILLS	45	Y	6	N	N	Y	GTCS	Y	Y	5	Not done	Not done	3	354	139	17	126	LYM	NORMAL	Y	10	DEATH	TB	2	2
37	62	4	M	8	2	LOW	N	44	Y	5	N	N	N	N	Y	N	4	Not done	Not done	3	573	143	13	125	LYM	NORMAL	N	13	IMP	TB	2	2
38	53	4	M	11	2	LOW	N	47	Y	3	N	N	Y	GTCS	Y	Y	4	Not done	Not done	3	355	148	17	130	LYM	NORMAL	Y	16	DEATH	TB	2	2
39	57	4	M	7	1	LOW	CHILLS	42	N	N	Y	PRO	N	N	Y	N	6	Not done	Not done	3	154	140	10	126	LYM	TUBERCULOMA	N	11	IMP	TB	2	2
40	66	4	M	10	2	LOW	CHILLS	42	Y	3	N	N	N	N	Y	Y	4	Not done	Not done	3	356	143	13	130	LYM	TUBERCULOMA	N	7	IMP	TB	2	2
41	71	4	M	6	1	LOW	N	48	N	N	N	N	Y	GTCS	Y	N	4	Not done	Not done	3	546	144	12	121	LYM	TUBERCULOMA	Y	13	IMP	TB	2	2
42	62	4	M	9	2	LOW	N	40	Y	5	Y	PRO	N	N	N	N	6	Not done	Not done	3	245	140	15	127	LYM	TUBERCULOMA	N	9	IMP	TB	2	2
43	56	4	F	13	2	LOW	CHILLS	45	Y	5	N	N	Y	GTCS	Y	Y	7	Not done	Not done	3	352	147	12	125	LYM	TUBERCULOMA	Y	16	DEATH	TB	2	2
44	46	3	M	9	2	LOW	CHILLS	47	Y	4	N	N	N	N	Y	Y	6	Not done	Not done	3	389	144	17	121	LYM	TUBERCULOMA	N	12	IMP	TB	2	2
45	55	4	F	11	2	LOW	CHILLS	44	Y	5	Y	PRO	N	N	Y	N	5	Not done	Not done	3	325	144	14	122	LYM	TUBERCULOMA	N	13	IMP	TB	2	2
46	43	3	M	7	1	LOW	CHILLS	42	Y	4	N	N	Y	GTCS	N	N	4	Not done	Not done	3	235	143	14	125	LYM	TUBERCULOMA	Y	12	IMP	TB	2	2
47	49	3	M	12	2	LOW	N	45	N	N	N	N	N	N	N	Y	7	Not done	Not done	3	466	139	16	121	LYM	TUBERCULOMA	N	9	IMP	TB	2	2
48	57	4	M	10	2	LOW	N	46	N	N	N	N	N	N	N	N	5	Not done	Not done	3	246	144	13	129	LYM	TUBERCULOMA	N	11	IMP	TB	2	2
49	71	4	M	11	2	LOW	N	42	N	N	N	N	N	N	Y	N	4	Not done	Not done	3	356	146	13	130	LYM	TUBERCULOMA	N	16	IMP	TB	2	2
50	58	4	M	9	2	LOW	N	47	Y	5	Y	PRO	N	N	Y	N	6	Not done	Not done	3	575	141	10	125	LYM	TUBERCULOMA	N	10	IMP	TB	2	2
51	43	3	M	9	2	LOW	N	44	Y	5	Y	PRO	N	N	N	N	7	Not done	Not done	3	464	142	13	121	LYM	TUBERCULOMA	N	8	IMP	TB	2	2
52	51	4	M	15	2	LOW	CHILLS	45	N	N	N	N	Y	GTCS	N	Y	4	Not done	Not done	3	256	145	15	125	LYM	TUBERCULOMA	Y	17	IMP	TB	2	2
53	63	4	F	7	1	LOW	N	48	N	N	N	N	N	N	Y	N	4	Not done	Not done	3	365	143	11	122	LYM	TUBERCULOMA	N	15	IMP	TB	2	2
54	49	3	F	12	2	LOW	N	42	Y	4	N	N	N	N	Y	N	5	Not done	Not done	3	573	139	18	129	LYM	TUBERCULOMA	N	13	IMP	TB	2	2
55	74	4	F	5	1	LOW	CHILLS	47	Y	4	N	N	N	N	Y	N	4	Not done	Not done	3	466	144	12	140	LYM	TUBERCULOMA	N	16	IMP	TB	2	2
56	66	4	M	4	1	LOW	N	45	N	N	N	N	Y	GTCS	N	N	4	Not done	Not done	3	245	142	15	129	LYM	TUBERCULOMA	Y	14	IMP	TB	2	2
57	58	4	M	11	2	LOW	N	44	N	N	Y	PRO	N	N	Y	N	7	Not done	Not done	3	235	148	17	120	LYM	TUBERCULOMA	N	15	IMP	TB	2	2
58	68	4	M	8	2	LOW	CHILLS	45	N	N	Y	PRO	N	N	Y	N	6	Not done	Not done	3	356	146	13	128	LYM	TUBERCULOMA	N	13	IMP	TB	2	2
59	59	4	F	7	1	LOW	N	47	Y	4	N	N	N	N	Y	Y	7	Not done	Not done	3	346	147	18	122	LYM	TUBERCULOMA	N	13	IMP	TB	2	2
60	43	3	F	9	2	HIGH	N	23	N	N	N	N	N	N	N	N	4	Not done	Not done	2	77	90	27	121	NEUT	MENIN	N	15	IMP	PYO	1	1
61	36	2	M	11	2	HIGH	CONTI	23	N	N	N	N	N	N	N	N	5	Not done	Not done	2	71	87	26	120	NEUT	MENIN	N	17	IMP	PYO	1	1
62	32	2	M	14	2	HIGH	CONTI	24	N	N	N	N	N	N	N	N	6	Not done	Not done	2	77	89	24	119	NEUT	MENIN	N	17	DEATH	PYO	1	1
63	35	2	M	5	1	HIGH	CONTI	23	N	N	N	N	N	N	N	N	6	Not done	Not done	2	73	88	24	119	NEUT	MENIN	N	17	IMP	PYO	1	1
64	34	2	M	9	2	HIGH	N	23	N	N	N	N	N	N	N	N	4	Not done	Not done	2	73	86	20	118	NEUT	MENIN	N	7	IMP	PYO	1	1
65	37	2	M	4	1	HIGH	N	23	N	N	N	N	N	N	N	N	6	Not done	Not done	2	77	83	24	122	NEUT	MENIN	N	10	DEATH	PYO	1	1
66	37	2	M	13	2	HIGH	N	24	N	N	N	N	N	N	N	N	5	Not done	Not done	2	77	83	27	119	NEUT	MENIN	N	15	IMP	PYO	1	1
67	34	2	M	6	1	HIGH	N	23	N	N	N	N	N	N	N	N	4	Not done	Not done	2	77	81	24	118	NEUT	MENIN	N	16	IMP	PYO	1	1

MASTER CHART

68	38	2	F	12	2	HIGH	CONTI	24	N	N	N	N	N	N	N	N	4	Not done	Not done	2	73	86	25	114	NEUT	MENIN	N	8	IMP	PYO	1	1
69	44	3	M	9	2	HIGH	CONTI	24	N	N	N	N	N	N	N	N	7	Not done	Not done	2	69	88	20	122	NEUT	MENIN	N	18	DEATH	PYO	1	1
70	32	2	F	8	2	HIGH	CONTI	24	N	N	N	N	N	N	N	N	7	Not done	Not done	2	77	90	26	124	NEUT	MENIN	N	13	DEATH	PYO	1	1
71	37	2	M	13	2	HIGH	CONTI	24	N	N	N	N	N	N	N	N	4	Not done	Not done	2	77	84	25	121	NEUT	MENIN	N	14	DEATH	PYO	1	1
72	39	2	F	14	2	HIGH	CONTI	23	N	N	N	N	N	N	N	N	6	Not done	Not done	2	72	85	24	114	NEUT	MENIN	N	18	DEATH	PYO	1	1
73	31	2	M	9	2	HIGH	N	23	N	N	N	N	N	N	N	N	7	Not done	Not done	2	73	87	27	115	NEUT	MENIN	N	10	IMP	PYO	1	1
74	37	2	M	11	2	HIGH	CONTI	23	N	N	N	N	N	N	N	N	5	Not done	Not done	2	68	91	24	118	NEUT	MENIN	N	15	IMP	PYO	1	1
75	34	2	F	7	1	LOW	N	24	N	N	N	N	N	N	N	Y	4	N	Not done	1	6	42	40	116	OCC NEUTRO	NORMAL	N	8	IMP	MALARIA	1	1
76	36	2	M	12	2	LOW	INTERMIT	25	N	N	N	N	N	N	N	N	6	Y	Not done	1	3	42	46	114	OCC NEUTRO	NORMAL	N	6	IMP	MALARIA	1	2
77	31	2	M	5	1	LOW	N	27	N	N	N	N	Y	GTCS	N	N	7	Y	Not done	1	4	45	43	127	OCC NEUTRO	NORMAL	Y	8	DEATH	MALARIA	1	2
78	29	1	M	12	2	LOW	INTERMIT	24	N	N	N	N	N	N	N	N	4	N	Not done	1	5	38	47	116	OCC NEUTRO	NORMAL	N	5	IMP	MALARIA	1	1
79	33	2	M	7	1	LOW	N	27	N	N	N	N	Y	GTCS	N	N	7	N	Not done	1	3	44	45	113	OCC NEUTRO	NORMAL	Y	8	IMP	MALARIA	1	2
80	32	2	M	9	2	LOW	N	25	N	N	N	N	Y	GTCS	N	N	4	Y	Not done	1	5	2	47	116	OCC NEUTRO	NORMAL	N	3	IMP	MALARIA	1	2
81	37	2	M	14	2	LOW	INTERMIT	27	N	N	N	N	N	N	N	N	6	N	Not done	1	43	38	42	119	OCC NEUTRO	NORMAL	N	8	IMP	MALARIA	1	2
82	38	2	M	8	2	LOW	INTERMIT	25	N	N	N	N	Y	GTCS	N	N	4	Y	Not done	1	4	37	51	118	OCC NEUTRO	NORMAL	Y	7	IMP	MALARIA	1	2
83	34	2	F	5	1	LOW	N	24	N	N	N	N	N	N	N	N	5	Y	Not done	1	4	41	47	118	OCC NEUTRO	NORMAL	N	12	IMP	MALARIA	1	1
84	40	2	M	6	1	LOW	INTERMIT	28	N	N	N	N	Y	GTCS	N	N	4	Y	Not done	1	3	41	48	112	OCC NEUTRO	NORMAL	Y	8	IMP	MALARIA	1	2
85	33	2	M	12	2	LOW	N	25	N	N	N	N	N	N	N	N	7	Y	Not done	1	2	36	52	120	OCC NEUTRO	NORMAL	N	5	IMP	MALARIA	1	2
86	38	2	M	14	2	LOW	INTERMIT	26	N	N	N	N	N	N	N	N	4	N	Not done	1	2	40	47	112	OCC NEUTRO	NORMAL	N	4	IMP	MALARIA	1	2
87	42	3	M	9	2	LOW	N	25	N	N	N	N	Y	GTCS	N	N	4	Y	Not done	1	5	35	42	120	OCC NEUTRO	NORMAL	Y	8	IMP	MALARIA	1	2
88	31	2	F	13	2	LOW	N	27	N	N	N	N	N	N	N	N	7	Y	Not done	1	3	44	53	116	OCC NEUTRO	NORMAL	N	4	IMP	MALARIA	1	2
89	39	2	M	9	2	LOW	N	24	N	N	N	N	Y	GTCS	N	N	5	N	Not done	1	4	44	46	116	OCC NEUTRO	NORMAL	Y	5	IMP	MALARIA	1	1
90	30	1	M	9	2	LOW	N	24	N	N	N	N	N	N	N	N	4	N	Not done	1	3	44	51	110	OCC NEUTRO	NORMAL	N	13	IMP	MALARIA	1	1
91	41	3	M	11	2	LOW	INTERMIT	24	N	N	N	N	N	N	N	N	5	N	Not done	1	2	40	43	116	OCC NEUTRO	NORMAL	N	16	DEATH	MALARIA	1	1
92	36	2	M	14	2	LOW	N	26	N	N	N	N	Y	GTCS	N	N	7	Y	Not done	1	5	39	47	120	OCC NEUTRO	NORMAL	Y	8	IMP	MALARIA	1	2
93	25	1	M	6	1	LOW	N	24	N	N	N	N	N	N	N	N	7	N	Not done	1	2	43	49	119	OCC NEUTRO	NORMAL	N	12	IMP	MALARIA	1	1
94	55	4	F	10	2	LOW	INTERMIT	26	N	N	N	N	N	N	N	N	6	Y	Not done	1	2	42	51	120	OCC NEUTRO	NORMAL	N	5	IMP	MALARIA	1	2
95	25	1	M	8	2	LOW	INTERMIT	24	N	N	N	N	Y	GTCS	N	N	4	N	Not done	1	2	40	47	120	OCC NEUTRO	NORMAL	Y	8	IMP	MALARIA	1	1
96	33	2	M	14	2	LOW	N	27	N	N	N	N	N	N	N	N	7	Y	Not done	1	5	37	42	117	OCC NEUTRO	NORMAL	N	4	IMP	MALARIA	1	2
97	31	2	M	10	2	LOW	INTERMIT	24	N	N	N	N	Y	GTCS	N	N	5	N	Not done	1	4	39	48	112	OCC NEUTRO	NORMAL	Y	6	IMP	MALARIA	1	1
98	26	1	M	11	2	LOW	N	24	N	N	N	N	N	N	N	N	5	Y	Not done	1	3	40	42	116	OCC NEUTRO	NORMAL	N	5	IMP	MALARIA	1	1
99	33	2	M	14	2	LOW	INTERMIT	27	N	N	N	N	N	N	N	N	7	N	Not done	1	5	38	47	111	OCC NEUTRO	NORMAL	N	8	IMP	MALARIA	1	2
100	30	1	M	12	2	LOW	INTERMIT	26	N	N	N	N	Y	GTCS	N	N	5	Y	Not done	1	4	38	41	119	OCC NEUTRO	NORMAL	Y	8	IMP	MALARIA	1	2