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Frequency of Hydrocephalus in patients with Tuberculous Meningitis

Najam Younas Butt[1]*, Yasir Malik[2], M Irshad[3]

1.2,3, Department of Neurology, Pakistan Institute of Medical Sciences, Islamabad. Pakistan.

Corresponding Author: Najam Younas, Department of Neurology, Pakistan Institute of Medical Sciences, Islamabad. Pakistan.

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Abstract

Introduction: *Tuberculosis can involve any organ system of the body. Tuberculosis of nervous system (NS) is not uncommon in our country. Tuberculous meningitis (TBM) is a severe form of extrapulmonary tuberculosis. In countries with high burden of pulmonary tuberculosis, the incidence of TBM is expected to be proportionately high. Common complications include SIADH, hydrocephalus, seizures and stroke. Here in this study I tried to look for hydrocephalus, so that early recognition and treatment of this complication may be carried out.*

Objective: *To determine the frequency of hydrocephalus in patients with tuberculous meningitis*

Study Design: *Cross sectional study.*

Duration of Study: *Six months (15th September, 2010 to 15th March, 2011)*

Materials and methods *This study was conducted in Neurology department of Pakistan Institute of Medical Sciences (PIMS), Islamabad. Nonprobability sampling technique was used. Patients with clinical features of TBM and having suggestive CSF were included and those with cerebral atrophy or congenital neurologic anomalies were excluded. All enrolled patients underwent brief history, clinical examination and CT scan of brain. Then approved proforma was filled by me. In the end data was analyzed in SPSS version 11.*

Results: *Sample size of 77 patients consisting of 47 male and 30 female patients was taken. Age of the patients ranged 14-72 years (mean=27.3), majority of patients were young. On CT scan brain 59 (76.6%) displayed hydrocephalus, amongst which 34 were male and 25 were female. Other than hydrocephalus tuberculomas were seen in 9 and infarction was seen in 14 patients. . CSF proteins were categorized and then compared with presence of hydrocephalus. All the patients with severely raised proteins had hydrocephalus, whereas 70.5% of the patients with moderately and 77% of the patients with mildly raised proteins exhibited hydrocephalus.*

Conclusion: *Hydrocephalus is a common complication of TBM. It is seen in 76.6% patients of TBM and it may be related to higher degree of CSF proteins.*

Key Wards: *Tuberculosis, Meningeal/complications, Hydrocephalus/etiology, Hydrocephalus/radiography.*

Tuberculosis most commonly involves lungs as primary site of infection but many other organs are potentially affected particularly central nervous system (CNS) .Intracranial tuberculosis has two related pathological processes: Tuberculous meningitis (TBM) and intracranial tuberculoma .The development of two pathologies is dependent on the site where Rich focus (tuberculous particle)rupture i.e. in subarachnoid space or brain parenchyma .

Currently, more than 2 billion people (ie, one third of the world's population) are infected with tuberculosis (TB), of which approximately 10% will develop clinical disease. The incidence of central nervous system (CNS) TB is related to the prevalence of TB in the community, and it is still the most common type of chronic CNS infection in developing countries

Despite great advances in immunology, microbiology, and drug development, TB remains among the great public health challenges.

Poverty; lack of functioning public health infrastructure; lack of funding to support basic research aimed at developing new drugs, diagnostics, and Vaccines; and the co-epidemic of HIV continue to fuel the ongoing epidemic of TB .

TBM may have an acute presentation .Fever ,headache ,signs of meningeal irritation and cranial nerve palsies are major presenting features of TBM in adults [1].Pacs BF etal described common presentations in pediatric group are weight loss (91%),loss of consciousness(96%),motor deficit(63%),meningial irritation(98%),raised intracranial pressure(23%),brainstem dysfunction(39%) and cranial nerve palsies(27%)[2].Sequelae of TBM include seizures,development delay,stroke ,stroke,syndrome of inappropriate Antidiuretic hormone secretion (SIADH) and hydrocephalus.

TBM continues to pose a diagnostic problem.. TBM should be a strong consideration when a patient presents with a clinical picture of meningoencephalitides, especially in high-risk groups. Diagnostic confusion often exists between TBM and other meningoencephalitides, in particularly partially treated

meningitis. TBM must be differentiated not only from other forms of acute and subacute meningitis but also from conditions such as viral infections and cerebral abscess.

The diagnosis of TBM cannot be made solely on the basis of clinical findings. Tuberculin testing is of limited value. Variable natural history and accompanying clinical features of TBM hinder the diagnosis. Spinal tap carries some risk of herniation of the medulla in any instance when intracranial pressure (ICP) is increased.

Early treatment is essential; death may occur as a result of missed diagnoses and delayed treatment. Antimicrobial therapy is best started with isoniazid, rifampin, pyrazinamide; addition of a fourth drug is left to local choice.

Hydrocephalus occurs in 85% cases of tuberculous meningitis [3], which is of two types communicating and obstructive. Communicating type is much more frequently seen in comparison to obstructive.In patients with evidence of obstructive hydrocephalus and neurological deterioration who are undergoing treatment for TBM, placement of a ventricular drain or ventriculoperitoneal or ventriculoatrial shunt should not be delayed.

Early shunting of hydrocephalus is the best option to prevent long term sequelae of TBM [4].All clinical and radiological parameters show regression in hydrocephalus after shunting [5].Endoscopic third ventriculostomy is another available solution of hydrocephalus, which has shown promising results in hydrocephalus of chronic tuberculous meningitis.

Tuberculous meningitis is a common disease of our society but unfortunately it is rarely worked upon. I planned to conduct a study on frequency of hydrocephalus as a result of TBM, so that hydrocephalus may be identified in early stage and complications of chronic TBM may be avoided by early shunting.

Meningitis

Definition of meningitis:

Meningitis is an inflammatory disease of the leptomeninges, the tissues surrounding the brain and spinal cord, and is defined by an abnormal number of white blood cells in the cerebrospinal fluid (CSF). The meninges consist of three parts: the pia, arachnoid, and dura maters. Bacterial meningitis reflects infection of the arachnoid mater and the CSF in both the subarachnoid space and the cerebral ventricles.

Bacterial meningitis was originally recognized in 1805 until the early 1900s it was virtually 100 percent fatal. In 1913, Flexner's introduction of intrathecal meningococcal antiserum prevented some deaths, but the clinical outcome did not dramatically improve until the introduction of systemic antimicrobial therapy in the 1930s.

Incidence and Epidemiology of bacterial meningitis.

Approximately 1.2 million cases of bacterial meningitis occur annually worldwide [6] [Meningitis is among the infectious causes of death and is responsible for approximately 135,000 deaths throughout the world each year. Neurologic sequelae are common among survivors.

The epidemiology of bacterial meningitis has changed dramatically over the last 20 years, primarily as a result of the introduction of conjugate vaccines against the common meningeal pathogens, such that in the developed world where vaccination is routinely utilized, bacterial meningitis has become a disease of adults rather than of infants and children [7].

Bacterial meningitis is an important cause of childhood morbidity and mortality world-wide. In the developing world, where the burden of acute meningitis and its long-term sequelae are especially high, staff with limited training at primary health care facilities must be able to recognize the symptoms and signs of meningitis, so that suspected cases can be referred urgently to hospitals [8]

A number of studies have evaluated the prevalence of different organisms that cause bacterial meningitis. The results vary based upon the type of infection: community-acquired, nosocomial, or recurrent.

Etiology of Bacterial Meningitis

Bacterial meningitis can be community-acquired or healthcare-associated

Community – Acquired Meningitis

The frequency of the different etiologic organisms of bacterial meningitis varies with age. The major causes of community-acquired bacterial meningitis in adults in developed countries are Streptococcus pneumoniae, Neisseria meningitides (N. meningitides), and, primarily in patients over age 50 to 60 years or those who have deficiencies in cell-mediated immunity, Listeria monocytogenes. Meningococcal meningitis is a potentially fatal disease which can affect many 15- to 24-year-old. that could have been protected from the disease if they had received the vaccination.[9]

Bacterial Meningitis remains a serious disease associated with substantial morbidity and mortality. Most cases are community acquired with S. Pneumoniae being the most common pathogen. Old age, diabetes mellitus, a positive culture, seizures as a complication and late stage in the disease are the important predictors of a poor outcome.[10]

A multicenter study of patients with bacterial meningitis in the United States in 1995 showed that the frequency of the major pathogens varies with age

- In adults up to age 60, S. pneumoniae was responsible for 60 percent of cases, followed by N. meningitidis (20 percent), H. influenzae (10 percent), L. monocytogenes (6 percent), and group B streptococcus (4 percent).
- In adults age 60 and above, almost 70 percent of cases were due to S. pneumoniae, approximately 20 percent to L. monocytogenes, and 3 to 4 percent each to N. meningitidis, group B streptococcus, and H. influenzae. An increased prevalence of L. monocytogenes in elderly adults has been noted in other reports as well.
- Meningitis due to infection with Mycobacterium Tuberculosis is more common in those from countries where Tuberculosis is common, but is also encountered in those with immune problems, such as HIV infected patients.

Nosocomial Meningitis

Healthcare-associated bacterial meningitis may occur after neurosurgical procedures, head trauma, and following placement of external or internal ventricular catheters. The likely microorganisms that cause meningitis in this setting (ie, staphylococci and gram-negative bacilli) are nnnmdifferent from those that cause meningitis in the community setting.[11]

Perioperative bacterial meningitis after trans-sphenoidal surgery for pituitary and parasellar lesions is an uncommon but serious complication [12]. PCNSI most commonly manifests as meningitis, subdural empyema, and/or brain abscess [13].Most frequent organisms are Gram-negative bacilli,streptococci, Staphylococcus aureus, and coagulase-negative staphylococci.

Recurrent bacterial meningitis:

Recurrent meningitis is caused by persisting anatomical defects, either congenital or acquired. It may also occur in patients with internal or external ventricular drains, or following trauma (ie, cranial trauma or after basilar skull fracture with or without clinical evidence of leak of CSF).

Geographical Distribution of bacterial Meningitis:

The distribution of pathogens also depends upon the region of the world reporting cases of bacterial meningitis. As an example, epidemics of meningitis due to N. meningitidis are uncommon in the United States and Europe but occur throughout the developing world, particularly in sub-Saharan Africa which has been plagued by large epidemics of meningococcal meningitis for over a century,] leading to it being labeled the "meningitis belt"

Epidemics typically occur in the dry season (December to June), and an epidemic wave can last two to three years, dying out during the intervening rainy seasons. Meningococcal disease occurs in epidemics in areas where many people live together for the first time, such as army barracks during mobilization, college campuses and the annual Hajj pilgrimage.

Several factors have been associated with the development of epidemics in the meningitis belt. They include medical conditions (immunological susceptibility of the population), demographic conditions (travel and large population displacements), socioeconomic conditions (overcrowding and poor living conditions), climatic conditions (drought and dust storms), and concurrent infections (acute respiratory infections)

Predisposing Risk factors

There are specific factors that may predispose certain hosts to bacterial meningitis with a particular organism (table 2), the following factors also may increase the risk of bacterial meningitis.

- Recent exposure to someone with meningococcal or Hib meningitis.
- Recent infection (especially respiratory or otic infection).
- Recent travel to areas with endemic meningococcal disease, such as sub-Saharan Africa.
- Penetrating head trauma.
- CSF otorrhea (including congenital defects, such as Mondini dysplasia) or CSF rhinorrhea.
- Cochlear implant devices.
- Anatomic defects (eg, dermal sinus or urinary tract anomaly) or recent neurosurgical procedure (eg, ventricular shunt placement) may predispose to meningitis with Staphylococcus aureus, coagulase-negative staphylococcus, and enteric gram-negative organisms, such as Escherichia coli and Klebsiella species

Pathogenesis

Bacterial meningitis develops when virulence factors of the pathogen overcome host defense mechanisms. For the most common pathogens causing bacterial meningitis in adults (S. pneumoniae, Neisseria meningitidis), meningeal invasion is related to several virulence factors that allow the bacteria to colonize host mucosal epithelium, invade and survive within the bloodstream, cross the blood-brain barrier, and multiply within the CSF.Pathogenesis consists of the following three stages :

1. Colonization and invasion:

Colonization of the host mucosal epithelium is facilitated by evasion of mucosal secretory IgA through pathogen secretion of IgA protease. IgA protease inactivates the mucosal antibody and facilitates bacterial attachment to host epithelial cells. After successful colonization, invasion occurs across the epithelium via intracellular or paracellular pathways that are mediated by specific binding adhesins of the bacterial surface, many of which are localized to pili in gram-negative pathogens.

2. Evasion of the complement system:

The next stage after invasion and entry into the bloodstream, bacteria survive through evasion of the complement system, particularly the alternative complement pathway. The bacterial capsular polysaccharide is the major mechanism for alternative complement evasion. As an example, the capsular sialic acid of N. meningitidis prevents binding of factor B to C3b and subsequent activation of the alternative pathway. For S. pneumoniae, C3b binds inefficiently to factor B on the capsular surface. In either case, the pathogens avoid the bactericidal activity of complement, survive in the bloodstream, and cross the blood-brain barrier into the CSF. 3.Entry into the cerebrospinal fluid.

The exact topographic site of bacterial entry into the CSF is unclear and may be distinct for different pathogens. For some pathogens such as Escherichia coli, experimental evidence suggests that CSF entry occurs at the choroid plexus and is facilitated by the presence of S. fimbriae on the bacterial surface.

After successful invasion of the CSF, bacteria can multiply to high concentrations (eg, up to 10(7) organisms per milliliter) because of inadequate humoral immunity in the CSF. Specifically, low concentrations of immunoglobulin and complement within human CSF result in poor opsonic activity, successful bacterial replication, and the subsequent development of inflammation.

Clinical presentation

In adults a severe headache is the most common symptom of meningitis – occurring in almost 90% of cases of bacterial meningitis, followed by nuchal rigidity. The classic triad of diagnostic signs consists of nuchal rigidity, sudden high fever, and altered mental status; however, all three features are present in only 44–46% of all cases of bacterial meningitis.

In adults patients presenting with community-acquired acute bacterial meningitis, the sensitivity of the classic triad of fever, neck stiffness, and altered mental status is low, but almost all present with at least two of the four symptoms of headache, fever, neck stiffness, and altered mental status [14] .

In addition to the classic findings, a number of other manifestations, both neurologic and non-neurologic, can occur in patients with bacterial meningitis, and some findings may be suggestive of a particular bacterial etiology.

- Neurologic complications such as seizures, focal neurologic deficits (including cranial nerve palsies), and papilledema may be present early or occur later in the course. Seizures have been described in 15 to 30 percent nts and focal neurologic deficits in 10 to 35 percent. Hearing loss is
- A late complication. Papilledema is observed in <5 percent of patients at the time of initial presentation.
- Patients with Listeria meningitis have an increased tendency to have seizures and focal neurologic deficits early in the course of infection, and some patients may present with a syndrome of rhombencephalitis (manifested as ataxia, cranial nerve palsies, and/or nystagmus).
- N. meningitidis, can cause characteristic skin manifestations, such as petechiae and palpable purpura.

Examination for nuchal rigidity:

Tests for examination of nuchal rigidity (such as Kernig's and Brudzinski's signs) were originally developed and tested in patients with severe, late stage meningitis (such as that caused by tuberculosis).

- The classic Brudzinski's sign refers to spontaneous flexion of the hips during attempted passive flexion of the neck.
- The Kernig's sign refers to the inability or reluctance to allow full extension of the knee when the hip is flexed 90º. Kernig's test is usually performed in the supine position, but it can be tested in the seated patient.

Diagnosis of Bacterial Meningitis:

Laboratory studies —In Routine lab work is often unrevealing. The white blood cell count is usually elevated, with a shift toward immature forms; however, severe infection can be associated with leukopenia. The platelet count may also be reduced. Leukopenia and thrombocytopenia have correlated with a poor outcome in patients with bacterial meningitis.

Coagulation studies may be consistent with disseminated intravascular coagulation. Results of serum chemistry tests are usually commensurate with the severity of the overall process and may reveal an anion gap metabolic acidosis or hyponatremia.

Blood cultures — Blood cultures are often positive and can be useful in the event that CSF cannot be obtained before the administration of antimicrobials.

Approximately 50 to 90 percent of patients with bacterial meningitis have positive blood cultures.

Cultures obtained after antimicrobial therapy are much less likely to be positive, particularly for meningococcus. Two sets of blood cultures should be obtained from all patients prior to the initiation of antimicrobial therapy.

Cerebrospinal fluid (CSF) analysis:

The usual CSF findings in patients with bacterial meningitis are a white blood cell count of 1000 to 5000/microL (range of <100 to >10,000) with a percentage of neutrophils usually greater than 80 percent, protein of 100 to 500 mg/dL, and glucose <40 mg/dL.

CSF analysis is an important diagnostic tool to differentiate acute bacterial from viral meningitis. Furthermore, when Gram stain and culture are negative, the CSF lactate can provide pertinent, rapid and reliable diagnostic information in distinguishing bacterial from viral meningitis[15] .

Clinicians must recognize that many exceptions exist, and that empiric antibiotic therapy is warranted when bacterial meningitis is suspected clinically even if the CSF abnormalities are not diagnostic.

Pleocytosis:

It is important to note that a false-positive elevation of the CSF white blood cell count can be found after traumatic lumbar puncture, or in patients with intracerebral or subarachnoid hemorrhage in which both red blood cells and white blood cells are introduced into the subarachnoid space. IGeneralized

seizures may also induce a transient CSF pleocytosis (primarily neutrophilic), although the CSF WBC count should not exceed 80/microL in this setting.

Gram stain

A Gram stain should be obtained whenever there is suspicion of bacterial meningitis. It has the advantage of suggesting the bacterial etiology one day or more before culture results are available. The following findings may be seen.

- Gram-positive diplococci suggest pneumococcal infection
- Gram-negative diplococci suggest meningococcal infection
- Small pleomorphic gram-negative coccobacilli suggest Haemophilus influenzae infection
- Gram-positive rods and coccobacilli suggest listerial infection

The Gram stain is positive in 10 to 15 percent of patients who have bacterial meningitis but negative CSF cultures. As noted above, the yield of both Gram stain and culture may be reduced by prior antibiotic therapy.

Lumbar Puncture.

A Lumbar puncture (LP) also known as a spinal tap is a diagnostic as well as therapeutic procedure that is performed in order to collect a sample of cerebrospinal fluid (CSF) for biochemical, mirobiological, and cytological analysis, or as a treatment to relieve increased intracranial pressure.

The most common indication for a lumbar puncture is to collect cerebrospinal fluid in a case of suspected meningitis, since there is no other reliable tool with which meningitis, a life-threatening but highly treatable condition, can be excluded.

Indications for CT scan before LP

Every patient with suspected meningitis should have CSF obtained unless lumbar puncture (LP) is contraindicated. It is not uncommon for LP to be delayed while a computed tomographic (CT) scan is performed to exclude a mass lesion or increased intracranial pressure, which rarely leads to cerebral herniation during subsequent CSF removal.

Based upon these observations and in agreement with the 2004 Infectious Diseases Society of America (IDSA) guidelines for the management of bacterial meningitis, a CT scan of the head before LP should be performed in adult patients with suspected bacterial meningitis who have one or more of the following risk factors.

- Immunocompromised state (eg, HIV infection, immunosuppressive therapy, solid organ or hematopoietic stem cell transplantation)
- History of CNS disease (mass lesion, stroke, or focal infection)
- New onset seizure (within one week of presentation)
- Papilledema.
- Abnormal level of consciousness.

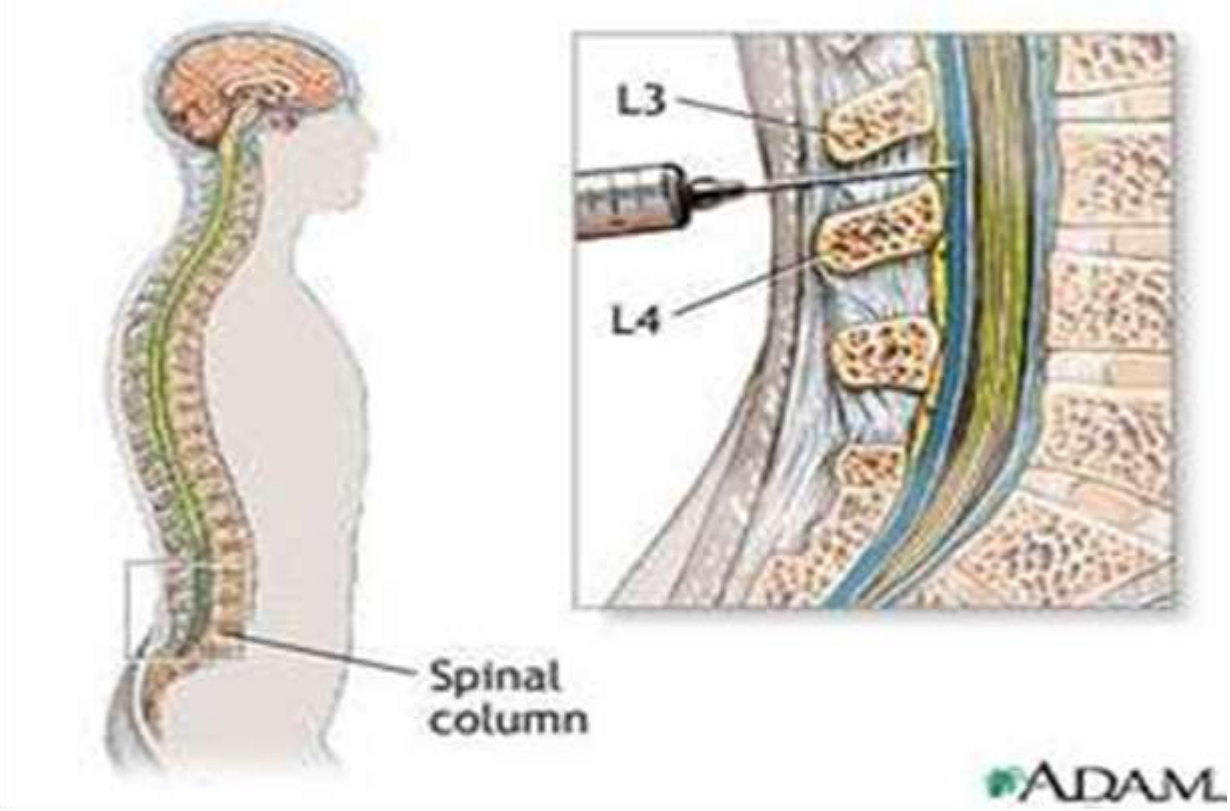

Figure 1. Anatomy of Lumbar Puncture

Complications of bacterial meningitis

Complications due to bacterial meningitis can be divided into systemic and neurologic. Systemic complications such as septic shock, disseminated intravascular coagulation, acute respiratory distress syndrome, and septic or reactive arthritis, are usually the consequence of the bacteremia that frequently accompanies meningitis.

The neurologic complications of bacterial meningitis include:

- Impaired mental status
- Increased intracranial pressure and cerebral edema
- Seizures
- Focal neurologic deficits (eg, cranial nerve palsy, hemiparesis)
- Cerebrovascular abnormalities
- Sensorineural hearing loss
- Intellectual impairment

Treatment of bacterial meningitis

Bacterial meningitis is a medical emergency, and immediate steps must be taken to establish the specific cause and initiate effective therapy. The mortality rate of untreated disease approaches 100 percent and, even with optimal therapy, there is a high failure rate.

Antibiotic therapy should be initiated immediately after the performance of the lumbar puncture (LP) or, if a computed tomography scan is to be performed before LP, immediately after blood cultures are obtained

Empiric antibiotic therapy should be initiated before cranial computed tomography. Adjuvant dexamethasone therapy initiated with or prior to the antibiotic therapy reduces mortality and morbidity for patients with pneumococcal meningitis without increasing the rate of side effects16.

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

Tuberculous meningitis

Central nervous system (CNS) tuberculosis (TB) includes three clinical categories: Tuberculous meningitis, intracranial tuberculoma, and spinal tuberculous arachnoiditis. Tuberculous meningitis is the most severe manifestation of extrapulmonary tuberculosis with a high mortality rate and a high rate of sequelae among survivors.[17]

The hallmark pathological processes are meningeal inflammation, basal exudates, vasculitis and hydrocephalus. Headache, vomiting, meningeal signs, focal deficits, vision loss, cranial nerve palsies

and raised intracranial pressure are dominant clinical features. Diagnosis is based on the characteristic clinical picture, neuroimaging abnormalities and cerebrospinal fluid changes. Early diagnosis & prompt treatment is essential to avoid morbidity & mortality. Cerebrospinal fluid smear examination, mycobacterial culture or polymerase chain reaction is mandatory for bacteriological confirmation Prompt diagnosis and early treatment are crucial. Decision to start antituberculous treatment is often empirical.

WHO guidelines recommend a a prolonged treatment extended to 9 or 12 months. Resistance to antituberculous drugs is associated with a high mortality. Patients with hydrocephalus may need ventriculo-peritoneal shunting. Bacillus Calmette-Guérin(BCG)vaccination protects to some degree against tuberculous meningitis in children. Children with TBM who have been vaccinated with BCG appear to maintain better mentation and have a superior outcome as compared to the unvaccinated [18].

More research is urgently needed to better understand the pathogenesis of disease and to improve its clinical management and outcome. A major stumbling block is the absence of standardised diagnostic criteria. The different case definitions used in various studies makes comparison of research findings difficult, prevents the best use of existing data, and limits the management of disease.[19]

Incidence and Epidemiology

- **Incidence :**

The exact incidence and prevalence are not known. Tuberculous meningitis (TBM) is commonly found to occur in the developing countries endemic to tuberculosis [20]. Human immunodeficiency virus-infected patients have a high incidence of tuberculous meningitis [21]. In the United States and in most western countries, the incidence of tuberculous meningitis, which parallels the frequency of systemic tuberculosis has until recently decreased steadily since theSecond World War..

In developing countries, particularly in sub-Saharan Africa, recent estimates of the incidence of tuberculosis suggest that it is 25 times more frequent than in the United States, again largely because of the prevalence of HIV infection.

- **Age :**

Tuberculous meningitis occurs in persons of all ages but more frequent in young children. Pediatric tuberculosis of the central nervous system (CNS-TB) is a severe form of extrapulmonary TB. It is most common in children between 6 months and 4 years of age. CNS-TB can present as meningitis and/or tuberculoma [22]

Pathophysiology:

Tuberculous meningitis is usually caused by the acid-fast organism Mycobacterium tuberculosis. Scattered tuberculous foci (tubercles) are established in the brain, meninges, or adjacent bone during the bacillemia that follows primary infection or late reactivation TB elsewhere in the body.

The chance occurrence of a subependymal tubercle, with progression and rupture into the subarachnoid space, is the critical event in the development of tuberculous meningitis as decribed by Rich.

The spillage of tubercular protein into the subarachnoid space produces an intense hypersensitivity reaction, giving rise to inflammatory changes typically begin with a dense basal meningeal exudate often resulting from a "Rich focus" along the basal surface of the cerebrum or ventricular ependyma. This inflammatory exudate is made up of small and large mononuclear cells, including epithelioid cells, which also act as macrophages and may fuse to form Langhans' giant cells. Three features dominate the pathology and explain the clinical manifestations of tuberculous meninginitis23.

- Proliferative arachnoiditis, most marked at the base of the brain, produces a fibrous mass involving cranial nerves and penetrating vessels. Spinal arachnoiditis is one of the common and disabling complication of tuberculous meningitis (TBM).

In one study 16 patients were included with a diagnosis of probable or highly probable TBM with symptoms for less than 1 month; three had radiological evidence of spinal arachnoiditis. High cerebrospinal fluid protein appeared to be a risk factor for development of spinal arachnoiditis. MRI is sensitive to detect early spinal arachnoiditis. Earlier diagnosis may be helpful in management of spinal arachnoiditis in TBM [24].

- Vasculitis with resultant thrombosis and infarction involves vessels that traverse the basilar or spinal exudate or are located within the brain substance itself. Cerebral infarction (CI) is a serious complication of tuberculous meningitis (TBM) [24]. It can be asymptomatic or symptomatic, causing stroke. Multiple lesions are common and a variety of stroke syndromes may result,

involving the basal ganglia, cerebral cortex, pons, and cerebellum. Intracranial vasculitis is a common feature of autopsy studies and a major determinant of residual neurologic deficits. In one autopsy study of 27 cases, for example, phlebitis and varying degrees of arteritis were demonstrated in 22 cases, including eight patients with associated hemorrhagic cerebral infarction.

Stroke in tuberculous meningitis (TBM) occurs in 15-57% of patients especially in advance stage and severe illness. The majority of strokes may be asymptomatic because of being in a silent area, deep coma or associated pathology such as spinal arachnoiditis or tuberculoma [25].

In another study which concluded that stroke occurs in 45% of patients with TBM both in early and later stage, mostly in basal ganglia region, and predicts poor outcome at 3 months [26].

Cerebral infarction (CI) complicating tuberculous meningitis (TBM) is a major risk factor of permanent disability. The prevention of this complication is an important issue in the quality care of TBM patients27.Even when increased intracranial pressure is treated and full conventional therapy is commenced, cerebral ischemia can develop and is associated with a particularly poor prognosis [28]

- Hydrocephalus is one of the commonest complications of tuberculous meningitis (TBM) occurring in up to 85% of children with the disease 3. It is more severe in children than in adults. It could be either of the communicating type or the obstructive type with the former being more frequently seen. It results from extension of the inflammatory process to the basilar cisterns and impedance of CSF circulation and resorption. Obstruction of the aqueduct develops less frequently, from contraction of exudate surrounding the brainstem or from a strategically placed brainstem tuberculoma.
- Spinal cord. Compression and radiculopathies The spinal cord may be affected in a number of ways in the course of tuberculous infection. In addition to compressing spinal roots and cord, causing spinal block, the inflammatory meningeal exudate may invade the underlying parenchyma, producing signs of posterior and lateral column and spinal root.

Spinal cord symptoms may also accompany tuberculous oteomyelitis of the pine with compression of the cord by an epidural abscess, a mass of granulation tissue (Pott paraplegia).

- •Tuberculomas These are tumor-like masses of tuberculous granulation tissue, most often multiple but also occurring singly, that form in the parenchyma of the brain and range from 2 to 12 mm in diameter The larger ones may produce symptoms of a space-ccupyinglesion and periventricular ones may cause obstructive hydrocephalus.

Tuberculomas occur in young patients from high-risk countries. The anti-tuberculous drug regimen in this series was 2 months of isoniazid, rifampin, pyrazinamide and ethambutol, followed by at least 10 months of isoniazid and rifampin [29].

In developing countries countries they constitute from 5 to 30 percent of all intracranial mass lesions Because of their proximity to the meninges, the CSF often contains a small number of lymphocytes and increased protein (serous meningitis), but the glucose level is not reduced. Tuberculomas occurred in approximately 39% of the patients with TBM. TBM patients with or without tuberculomas had a similar prognosis [30]

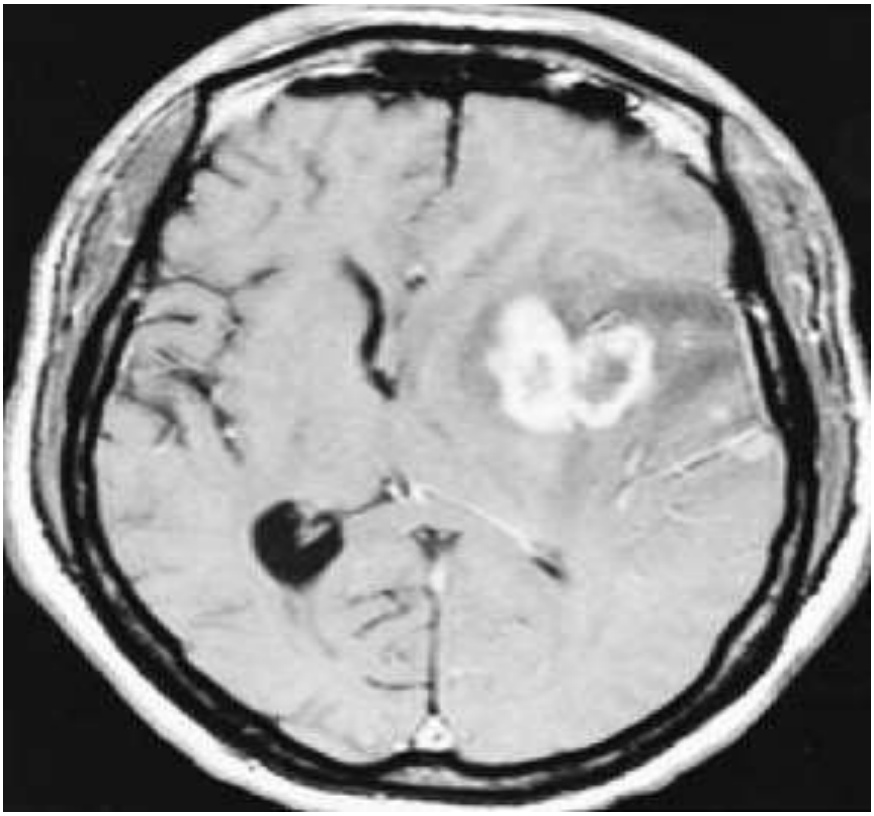

Figure 2. MRI in tuberculous meningitis. There is gadolinium enhancement of the basal meninges, reflecting intense inflammation that is accompanied by hydrocephalus and cranial nerve palsies.

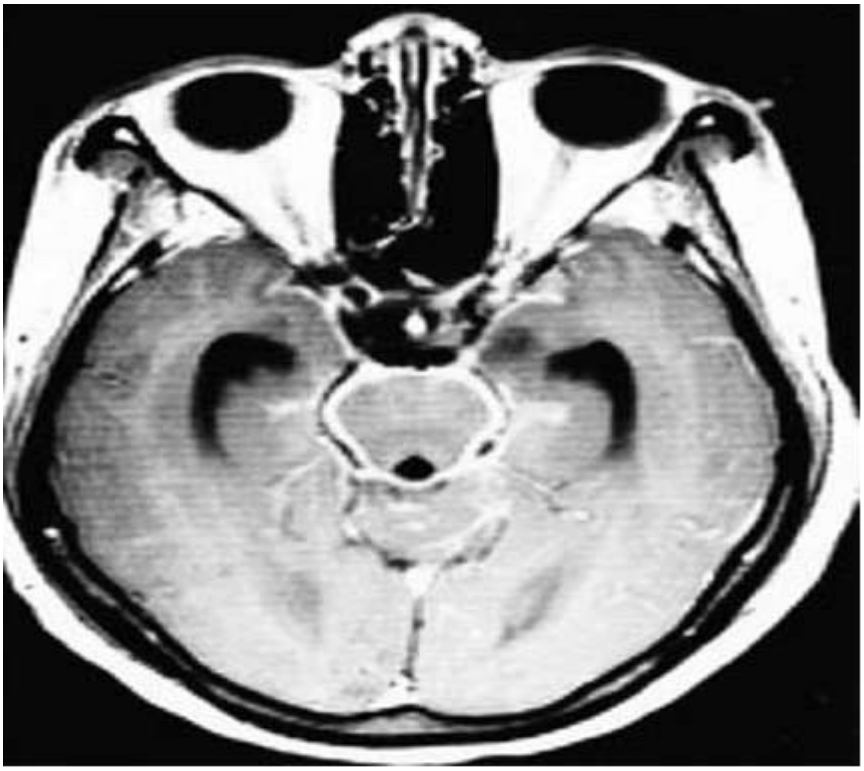

Figure 3. A tuberculoma of the deep hemisphere States. The mass behaved clinically like a primary malignant brain tumor and resembled a tumor on a gadolinium-enhanced MRI.

Clinical features

The usual patient with tuberculous meningitis presents with a subacute febrile illness that progresses through three discernible phases

- The prodromal phase, lasting two to three weeks, is characterized by low-grade fever, malaise, headache(more than one-half the cases), lethargy, confusion, and stiff neck(75 percent of cases), with Kernig and Brudzinski signs..
- The meningitic phase follows with more pronounced neurologic features, such as meningismus, protracted headache, vomiting, lethargy, confusion, and varying degrees of cranial nerve and long-tract signs.
- The paralytic phase is the stage during which the pace of illness may accelerate rapidly; confusion gives way to stupor and coma, seizures, and often hemiparesis. For the majority of untreated patients, death ensues within five to eight weeks of the onset of illness.

In approximately two-thirds of patients with tuberculous meningitis there is evidence of active tuberculosis elsewhere, usuallyin the lungs and occasionally in the small bowel, bone, kidney, or ear. In young children and infants, apathy, hyperirritability, vomiting and seizures are the usual symptoms.

In adult patients, HIV-infected patients have a high incidence of tuberculous meningitis.21 Untreatedillness is characterized by confusionand progressively deepening stupor and coma, coupledwith cranial nerve palsies, pupillary abnormalities, focal neurologicdeficits, raised intracranial pressure, and decerebrate postures;invariably, a fatal outcome then follows within 4 to 8 weeksof the onset.

A study was done to investigate child behaviour in children who recovered from tuberculous meningitis (TBM) and to compare behaviour profiles of stage II and stage III patients. Results showed that problems with conduct, attention, attention-deficit/hyperactivity problems, affective problems as well as the total problem scores were more pronounced in the patients with stage III TBM.

Finally concluded that general behavioural disinhibitions as well as internalized emotional disorder probably are long-term complications in more than 10% of the survivors of TBM.[31]

Deferential Diagnosis

Tuberculous meningitis (TBM) is a major global health problem, and it is sometimes difficult to perform a differential diagnosis of this disease from other diseases, particularly partially treated pyogenic meningitis (PTPM). Other differentials of tuberculous meningitis include subacute or chronic meningitis syndrome with a CSF formula characterized by a lymphocytic pleocytosis, lowered glucose concentration, and a high protein content. This is seen most commonly with cryptococcosis, occasionally with other deep-seated granulomatous fungal infections, brucellosis, and neurosyphilis. Patients with herpes encephalitis may exhibit a similar CSF formula, including mild lowering of CSF glucose concentration.

Early TBM often presents with atypical features and its differential diagnosis can be difficult. CSF monitoring and careful inspection of the radiographic data can be helpful in the diagnosis of suspected cases, for which early anti-TB treatment is an important means to reduce misdiagnosis [32]

Diagnosis

The diagnosis of tuberculous meningitis can be difficult. Maintaining a high degree of suspicion is vital in order to initiate therapy promptly.The most important investigation is the lumbar puncture, which preferably should be performed before the administration of antibiotics.

Cerebrospinal fluid examination

The cerebrospinal fluid (CSF) is usually under increased pressure and contains between 50 and 500 white cells per cubic millimeter,rarely more. Early in the disease there may be a atypical more or less equal number of polymorphonuclear leukocytes and lymphocytes; but after several days, lymphocytes predominate in the majority of cases. In one study Neutrophilic plecytosis at the first spinal tap was found in 32.4% of TBM patients, who had a worse outcome when compared with those patients with typical CSF profiles. [33]

The protein content of the CSF is always elevated, between 100 to 200 mg/dL in most cases, but much higher if the flow of CSF is blocked around the spinal cord. Glucose is reduced to levels below 40 mg/dL. Patients with definite TBM had significantly higher CSF protein, lower CSF glucose, higher CSF cell count and lower CSF lymphocytes [34]

HIV-infected patients had a higher frequency of non-inflammatory CSF (absence of pleocytosis) and of infection by multidrug-resistant strains of Mycobacterium tuberculosis. Protein CSF levels were lower in HIV-infected patients, while and glucose concentration was similar in both groups.

The diagnosis of TBM is often difficult. A reliable, costeffective and rapid diagnostic test, which can be performed in any standard pathology laboratory,could be of help in the diagnosis of TBM. In one study the Adenosine deaminase (ADA) activity in cerebrospinal fluid (CSF) of TBM and non-TBM patients was compared . The results showed that mean CSF ADA activity was found to be significantly higher in CSF of TBM patients, This study concluded that ADA activity in the CSF of TBM patients, using a cutoff value 11.39 U/L/min, can be useful for the early differential diagnosis of TBM. This test can be performed in any pathology laboratory where more sophisticated methods are not available [35].

In another study concentrations of pro- and anti-inflammatory cytokines in serial blood and cerebrospinal fluid (CSF) samples from 21 adults who were being treated for tuberculous meningitis were measured. Results showed that CSF concentrations of lactate, interleukin-8, and interferon-gamma were high before treatment and then decreased rapidly with antituberculosis chemotherapy.

Death was associated with high initial CSF concentrations of lactate, low numbers of white blood cells, in particular neutrophils, and low CSF glucose levels [36] .

Bacteriology

The conventional methods of demonstrating tubercle bacilli in the spinal fluid are inconsistent and often too slow for immediate therapeutic decisions. There are effective means of culturing the tubercle bacilli; but since their quantity is usually small, attention must be paid to proper technique.

Polymerase chain reaction (PCR)

The Polymerase chain reaction (PCR) is superior to the currently available techniques for the diagnosis of tuberculous meningitis in terms of sensitivity, specificity and rapidity and could play a critical role in the diagnosis of suspected cases [37]

The diagnosis of tuberculous meningitis (TBM) remains a complex issue because the most widely used conventional diagnostic tools, such as culture and PCR assay for cerebrospinal fluid (CSF) samples, are unable to rapidly detect Mycobacterium tuberculosis with sufficient sensitivity in the acute phase of TBM. for the rapid and accurate diagnosis of TBM, the quantitative nested real-time (QNRT-PCR) assay is a more useful and advanced technique as compared to the conventional PCR assay [38]

Neuroradiology

Computed tomography (CT) and magnetic resonance imaging (MRI) have improved greatly characterization and management of CNS infections.

CT scanning is used widely for making the diagnosis and detecting the complications of tuberculous meningitis (TBM) CT is particularly suggestive of the diagnosis when there is a combination of basal enhancement, hydrocephalus and infarction, and even then the diagnosis may be in doubt. [39],. In two large community-based series hydrocephalus was seen in approximately 75 percent of patients, basilar meningeal enhancement in 38 percent, cerebral infarcts in 15 to 30 percent, and tuberculomas in 5 to 10 percent [40].

In another study which showed that hydrocephalus and meningeal enhancement were the two commonest neuroimaging features. Other features include infarction, enhancing lesion, tuberculoma,

abcess, oedema and calcification. Contrasted CT scan is an adequate neuroimaging tool to unmask abnormal findings in tuberculous meningitis [41].

In a patient with compatible clinical features, CT evidence of basilar meningeal enhancement combined with any degree of hydrocephalus is strongly suggestive of tuberculous meningitis. The CT scan is normal in approximately 30 percent of cases with Stage I meningitis, and patients with a normal scan nearly always recover completely on therapy. Hydrocephalus combined with marked basilar enhancement is indicative of advanced meningitic disease and carries a poor prognosis. The presence of high density within the basal cisterns on non-contrast CT scans is a very specific sign for TBM in children [42]

Early follow-up CT is useful in making a diagnosis of TBM by demonstrating features that were not present initially and by demonstrating more sensitive, obvious or additional features of TBM. In addition, follow-up CT is valuable as a prognostic indicator as it demonstrates additional infarcts which may have developed or become more visible since the initial study. Lastly, follow-up CT has therapeutic value in demonstrating hydrocephalus, which may develop over time and may require drainage. Routine follow-up CT is advised in patients with suspected TBM within the first week of initial CT and optionally at 1 month [43].

In one study which showed comparison of Radiological features in HIV and non-HIV infected tuberculous meningitis (TBM) patients in. They concluded that HIV-infected children are less likely to display meningovascular enhancement, tuberculoma formation and obstructive hydrocephalus [44].

The characteristics of intracranial tuberculoma on computed tomography (CT) and magnetic resonance imaging (MRI) are not well known The MRI signal characteristics of intracranial tuberculoma are extremely diverse. An isointense or hypointense core with a hyperintense rim on T2-weighted and FLAIR images is the most common presentation. Core hypointensity of lesions on these images is related to necrosis and the large number of cells [45].

MRI is superior to CT for diagnosing TBM by detecting basal enhancement, tuberculomas and infarcts in strategic locations especially of the brainstem [46] MR angiography may demonstrate vascular occlusive disease from granulomatous infiltration of the walls of arteries of the circle of Willis and their primary branches. Cerebrospinal MRI performed when TBM is suspected aids in its diagnosis and is also a useful means of monitoring the course of the disease under treatment [47]. Reactive diffuse meningeal enhancement occurs in the early period of TBM on contrast medium-enhanced T1-weighted MR images, but later becomes limited to basal areas. [48]

Medical Treatment of Tuberculous Meningitis

Specific antituberculous therapy (ATT) should be initiated on the basis of strong clinical suspicion and should not be delayed until proof of infection has been obtained. Rapid diagnosis and early treatment before the occurrence of progression of stage are crucial for the outcome of TBM.

TBM may present with an acute course, and when discrimination from bacterial meningitis is difficult, it is mandatory to start antituberculosis and antibacterial therapy simultaneously.[49] The clinical outcome depends greatly on the stage at which therapy is initiated; much more harm results from delay, even for only a few days. TBM is an important public health issue and the emergence of resistant strains of this disease in recent years presents a therapeutic challenge. Because delay in diagnosis is directly related to poor outcome, early diagnosis and early treatment are essential for survival [50].

First line drugs

Isoniazid (INH), rifampin (RIF), and pyrazinamide (PZA) are bactericidal, can be administered orally, penetrate inflamed meninges, and achieve CSF levels that exceed the inhibitory concentration needed for sensitive strains.

Isoniazid (INH) INH has excellent CNS penetration and is more active against rapidly dividing than semidormant organisms. The initial dose is 10 mg/kg per day for adults and children, once a favorable response is achieved.

Isoniazid resistance on initial susceptibility testing was associated with subsequent death among cases of tuberculous meningitis with positive cerebrospinal fluid cultures. Randomised controlled trials are needed to evaluate the optimal empirical regimen for treating patients with tuberculous meningitis who are at high risk for both initial isoniazid resistance and poor clinical outcomes[51] .

Rifampin (RMP) is active against both rapidly dividing organisms and semidormant subpopulations of organisms. The dose is 10 mg/kg per day (600 mg in adults se should be reduced to 5 mg/kg (300 mg per day for adults.

Pyrazinamide: (PZA) readily penetrates the CSF and is highly active against intracellular mycobacteria. Within the dosing range of 15 to 30 mg/kg per day (maximum 2 g dose), PZA augments the regimen without added risk for hepatotoxicity when the drug's use is limited to two months.

Ethambutol: — Ethambutol (EMB) (15 to 25 mg/kg per day) achieves moderate CSF concentrations but carries the risk of optic neuritis at higher doses. Ocular toxicity is rare at the recommended dose

of 15 mg/kg per day. Patients receiving ethambutol should undergo baseline Snellen visual acuity and red-green color perception testing and should be referred to an ophthalmologist if visual complaints develop while on therapy.

Second line drugs

There are six classes of second-line drugs used for the treatment of TB.Second line drugs are less effective than the first-line drugs (e.g., p-aminosalicylic acid); or, it may have toxic side-effects (e.g., cycloserine);

- Aminoglycosides e.g., amikacin,kanamycin .
- Polypeptides : e.g., capreomycin, viomycin, enviomycin.
- Fluoroquinolones : e.g., ciprofloxacin , levofloxacin, moxifloxacin .
- Thioamides: e.g. ethionamide, prothionamide .
- Cycloserine(the only antibiotic in its class).
- P-aminosalicylic acid .

Recommended regimen

Intensive phase — A four drug regimen that includes INH, RMP, PZA, and either EMB or Streptomycin (STM) for two months followed by:

Continuation phase — INH and RMP alone if the isolate is fully susceptible, for an additional seven to 10 months.

Duration of therapy — We recommend that therapy be administered for nine to 12 months in drug-sensitive infections. If PZA is omitted or cannot be tolerated, treatment should be extended to 18 months.

The antituberculous chemotherapy regimen for clinical tuberculoma is the same as for meningitis, except that duration of treatment is extended to 18 months. Intracranial tuberculomas are known to develop within weeks or a couple of months after the start of antituberculous therapy (ATT).[52]

Drug-resistant M. tuberculosis:

CNS infection caused by strains resistant to one or more first line drugs is becoming increasingly prevalent. ; if the risk of INH resistance or multidrug resistance is higher, the use of ethionamide and

a fluoroquinolone and possibly cycloserine is recommended and pyrazinamide should be continued for full treatment duration. The penetration of RMP, ethambutol and streptomycin into cerebrospinal fluid is poor; higher dosages of RMP should be considered.[53]

Those most at risk for drug-resistant disease include individuals from areas of the world where TB is endemic, those with a history of previous antituberculous treatment, homeless persons, and those with exposure to source patients harboring drug-resistant organisms There are no guidelines for the duration of therapy in patients with multi-drug resistant infection. In such cases, it may be advisable to extend the duration of therapy to 18 to 24 months, taking into account the severity of illness, rate of clinical response, and the status of the patient's immune system.

Isoniazid resistance on initial susceptibility testing was associated with subsequent death among cases of tuberculous meningitis with positive cerebrospinal fluid cultures. Randomised controlled trials are needed to evaluate the optimal empirical regimen for treating patients with tuberculous meningitis who are at high risk for both initial isoniazid resistance and poor clinical outcomes .Rapidly progressive multidrug-resistant tuberculosis (MDR-TB) is well documented in human immunodeficiency virus (HIV) positive subjects, but it is not fully recognised in HIV-negative subjects in the familial environment.[54]

Paradoxical responses to intracranial tuberculoma/neurotuberculosis can occur at any time even up to 1 year during chemotherapy despite a regular standard antitubercular treatment.[55]

Glucocorticoids

Tuberculous meningitis (TBM) is characterized by disruption of the blood-brain barrier (BBB), cerebral edema and increased intracranial pressure (ICP). Vascular endothelial growth factor (VEGF) secreted by inflammatory cells is a potent vascular permeability factor and a mediator of brain edema.Corticosteroids act by inhibiting Vascular endothelial growth factor (VEGF) which may explain part of the clinical effect of adjuvant corticosteroid therapy in TBM.[56]

There is considerable experimental evidence and a growing base of clinical data that adjunctive glucocorticoid therapy is beneficial in both adults and children with tuberculous meningitis

A randomized, double-blind trial in Vietnam compared dexamethasone (for the first six to eight weeks of treatment in a tapering dose regimen) with placebo in 545 patients over 14 years of age [57]. The following findings were noted:

- Mortality was reduced significantly in the dexamethasone-treated group (32 versus 41 percent). The mortality benefit was most evident for patients with Stage I disease (17 versus 30 percent), approached significance for Stage II (31 versus 40 percent), and was not significant in patients with Stage III disease (55 versus 60 percent)
- There was no demonstrable reduction in residual neurologic deficits and disability among surviving patients evaluated by questionnaire at nine months follow-up.
- The survival benefit associated with steroid therapy may have been in part due to a reduction in severe adverse events (9.5 versus 16.6 percent), particularly hepatitis that necessitated changes in antituberculosis drug regimens.
- No mortality benefit from dexamethasone was evident in 98 HIV-infected patients included in the study.

In another study the effect of dexamethasone on cerebral MRI changes and their association with intracerebral inflammatory responses and clinical outcome in adults treated for tuberculous meningitis was determined..This study concluded that dexamethasone may affect outcome from tuberculous meningitis by reducing hydrocephalus and preventing infarction [58].

Role of Aspirin in Tuberculous meningitis

Aspirin play a significant role in tuberculous meningitis as supported by a study which includes 118 TBM patients were randomized into aspirin and placebo groups. The baseline demographic, clinical (severity of meningitis, MRI and CSF changes) were not significantly different between the two groups. 19 (16.1%) patients lost from follow up. 21 (33.3%) patients developed stroke after randomization which was

Insignificantly lesser in aspirin (24.2%) compared to the placebo group (43.3%; OR 0.42, 95%CI 0.12-1.39). Aspirin resulted in absolute risk reduction of stroke in 19.1% and significant reduction in mortality compared to placebo (21.7% Vs 43.4%, P=0.02). Aspirin resulted in insignificantly lesser strokes and significantly reduced 3 month mortality in patients with TBM [59].

Surgical Management:

There is a significant role of surgery in patients of Tuberculous meningitis with hydrocephalus by surgical decompression of the ventricular system in order to effectively manage the complications of

raised intracranial pressure. In such patients with clinical stage II disease, the combination of serial lumbar puncture and steroid therapy may suffice while judging the early response to chemotherapy.

Unlike other CNS mass lesions, medical management is preferred for clinical tuberculomas, as surgical removal has often been complicated by severe fatal meningitis, unless the lesion produces obstructive hydrocephalus or compression of the brainstem. In the past, surgical resection was often complicated by severe, fatal meningitis.

Prognosis of Tuberculous Meningitis:

Significant prognostic factors included severity of TBM at the time of admission, the presence of headache, fever, hydrocephalus, high CSF protein concentration and high CSF lactate concentration. In stepwise logistic regression analysis, only the presence of hydrocephalus and severity of TBM on admission were strongly associated with therapeutic failure even after adjusting for other potentially confounding factors [51].

Old age, advanced stage of TBM at admission, hydrocephalus, and positive TB culture or polymerase chain reaction of CSF are factors associated with a poor prognosis for TBM. Early diagnosis and treatment, including short term steroid use, are mandatory for clinical care of adult patients with TBM [60].

Vision impairment occurred in one-fourth of patients with tuberculous meningitis. Principal causes of vision loss were optochiasmatic arachnoiditis and optochiasmal tuberculoma. Impaired vision predicted death or severe disability [61]

Several clinical and laboratory features of TBM in patients who are HIV-positive are distinctly different from those without HIV infection; some of these have an association with the probability of adverse outcome [62].

Successful treatment of TBM requires a combination of antimicrobial agents, with vigilance regarding the possibility of disease caused by resistant organisms. Adjunctive corticosteroids also have a role in treating this potentially devastating infection, as can neurosurgery. With proper therapy, morbidity and mortality can be minimized in patients with TBM [63].Early antimycobacterial therapy and close monitoring of TBM in childhood improve the outcome [64].

Tuberculous meningitis remains a serious health threat in developing countries. The variable (clinical features and laboratory investigations) of TBM had significant capacity for the early diagnosis if

applied scientifically. There is an urgent need to improve diagnostic services at primary and secondary level to reduce the TBM stage III [65].

HIV-associated tuberculous meningitis (TBM) poses significant diagnostic and therapeutic challenges and carries poor prognosis In HIV-associated TBM, clinical course and outcome are influenced by profound immunosuppression at presentation, emphasising the need for earlier diagnosis of HIV infection and initiation of antiretroviral treatment [66].

Hydrocephalus:

Introduction

Hydrocephalus can be defined as a disorder in which the cerebral ventricular system contains an excessive amount of cerebrospinal fluid (CSF) and is dilated because of increased pressure. Hydrocephalus is one of the commonest complications of tuberculous meningitis (TBM) occurring in up to 85% of children with the disease. It is more severe in children than in adults3. The increased pressure distinguishes hydrocephalus from atrophy, in which dilatation is due to loss of brain tissue.

Cerebrospinal fluid (CSF) accumulates due to an imbalance between production and absorption. Hydrocephalus upon presentation is common in TBM patients. This may be a poor prognostic marker associated with severe TBM and a higher risk of stroke [67].

Physiology of Cerebrospinal Fluid (CSF):

a. CSF Production:

CSF is produced primarily by the choroid plexus. It circulates through the ventricular system and is absorbed into the systemic circulation. Choroid plexus tissue is located in the cerebral ventricles. It consists of villous folds lined by epithelium with a central core of highly vascularized connective tissue. The choroid plexus produces CSF by active secretion and diffusion.

The production rate of CSF in adults is approximately 20 mL/hour, which results in complete turnover of the CSF three or four times per day. The CSF production rate is less in newborns and young children, although few studies are available. In one report, the hourly output of CSF from external ventricular drains (placed primarily for shunt infection) was measured in children with hydrocephalus [68].

The total volume of CSF in infants is approximately 50 mL, compared to approximately 150 mL in normal adults [8]. In adults, 25 percent is within the ventricular system.

CSF formation continues when the intracranial pressure rises, unless extremely high levels are reached. Thus, there must be some absorption of fluid to accommodate the volume of CSF being formed each day.

b. Ventricular system:

The ventricular system is comprised of a pair of lateral ventricles that each connect through an interventricular foramen (of Monro) to the midline third ventricle (figure 1). The third ventricle is connected to a midline fourth ventricle by the cerebral aqueduct (of Sylvius). Three exits from the fourth ventricle, the paired lateral foramina of Luschka and a midline foramen of Magendie, lead to a system of interconnecting and focally enlarged areas of subarachnoid spaces known as cisterns.

The cisterns in the posterior fossa connect to the subarachnoid spaces over the cerebral convexities through pathways that cross the tentorium. The basal cisterns connect the spinal and intracranial subarachnoid spaces.

c. CSF absorption: CSF flows from the lateral ventricles to the third and fourth ventricles and then through the basal cisterns, tentorium, and subarachnoid space over the cerebral convexities to the area of the sagittal sinus. The net flow of CSF in the spinal subarachnoid space is cephalad.

CSF is absorbed into the systemic circulation primarily across the arachnoid villi into the venous channels of the sagittal sinus. Some CSF absorption also occurs across the ependymal lining of the ventricles and from the spinal subarachnoid space.

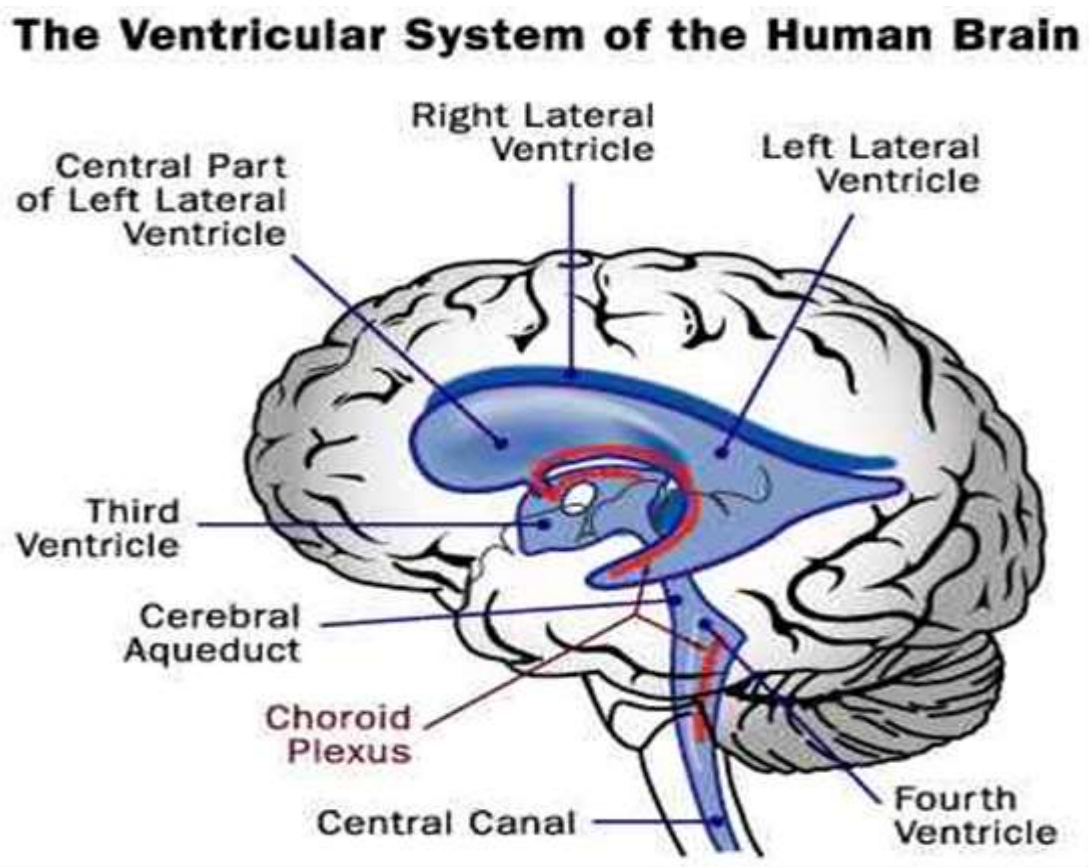

Figure 4. Anatomy of Ventricular system

Pathogenesis

Three mechanisms can explain the imbalance between CSF formation and absorption that leads to hydrocephalus: obstruction of CSF pathways, impaired venous absorption, and oversecretion of CSF.

Obstruction: Anatomic or functional obstruction to CSF flow is the most common mechanism of hydrocephalus. The obstruction occurs at the foramen of Monro, the aqueduct of Sylvius, or the fourth ventricle and its outlets. Dilatation of the ventricular system occurs proximal to the block. Obstruction of one foramen of Monro results in dilatation of the lateral ventricle on that side. If the aqueduct of Sylvius is blocked, the lateral and third ventricles dilate, while the size of the fourth ventricle remains relatively normal.

Impaired absorption: A less common mechanism is impaired venous absorption which is typically due to inflammation of the subarachnoid villi. This results in communicating hydrocephalus, in which the entire ventricular system is dilated.

Excessive production: Excessive production of CSF is a rare cause of hydrocephalus. This condition may occur with a functional choroid plexus papilloma and leads to enlargement of the entire ventricular system.

Types of Hydrocephalus

Hydrocephalus is of three types:

1. Obstructive hydrocephalus ; The disorder that results from obstruction of the ventricular system is known as obstructive, or noncommunicating, hydrocephalus.
2. Communicating hydrocephalus : This condition occurs when the subarachnoid pathways are blocked. CSF production is nearly always normal.also occurs across the ependymal lining of the ventricles and from the spinal subarachnoid space.
3. Complex hydrocephalus: This disorder is characterized by the combination of both obstruction of the ventricular system and impaired absorption of cerebrospinal fluid (CSF) .

Pathophysiology

Acute obstruction to CSF flow causes increased pressure and rapid enlargement of the ventricular system. The frontal and occipital horns of the lateral ventricles enlarge first. Symmetric dilatation of the remainder of the intracerebral CSF-containing spaces follows.

Increasing pressure results in flattening of the gyri and compression of the sulci against the cranium, obliterating the subarachnoid space over the hemispheres. The vascular system is compressed, and the venous pressure in the dural sinuses increases. Ventricular enlargement results in thinning of the cerebral mantle, although the total mass of brain tissue is initially unchanged.

Ventricular enlargement also disrupts the ependymal lining of the ventricular system, allowing CSF to move directly into brain tissue. This is an alternate route of CSF absorption that may limit further dilatation. However, it contributes to the development of interstitial edema of the periventricular white matter.

Another compensatory mechanism that limits expansion of the ventricular system in infants is spreading of the cranial sutures. Intracranial pressure may be less in chronic hydrocephalus than in the acute state because the force of the fluid is distributed over the greater surface area of the enlarged ventricular system.

Etiology of Hydrocephalus

Hydrocephalus can be congenital or acquired. Both categories include a diverse group of conditions..

A. Congenital Hydrocephalus

Congenital hydrocephalus results from CNS malformations (which include nonsyndromic and syndromic disorders, infection, trauma, and teratogens . A rare cause of hydrocephalus is obstruction caused by a congenital CNS tumor, especially if located near the midline.Following are the conditions associated with congenital hydrocephalus:

Neural tube defects:

The majority of patients with myelomeningocele have hydrocephalus. The etiology is obstruction of fourth ventricular outflow or flow of CSF through the posterior fossa due to the Chiari malformation or an associated aqueductal stenosis

Isolated hydrocephalus:

Isolated hydrocephalus is frequently caused by aqueductal stenosis. This can be due to congenital narrowing of the aqueduct, or result from inflammation due to intrauterine infection.

X-linked hydrocephalus:

The most common genetic form of congenital hydrocephalus is X-linked hydrocephalus with stenosis of the aqueduct of Sylvius (HSAS) . Approximately 50 percent of affected boys have adducted thumbs, which is helpful in making the diagnosis. Some have other CNS abnormalities such as agenesis or dysgenesis of the corpus callosum, small brainstem, or absence of the pyramidal tract.

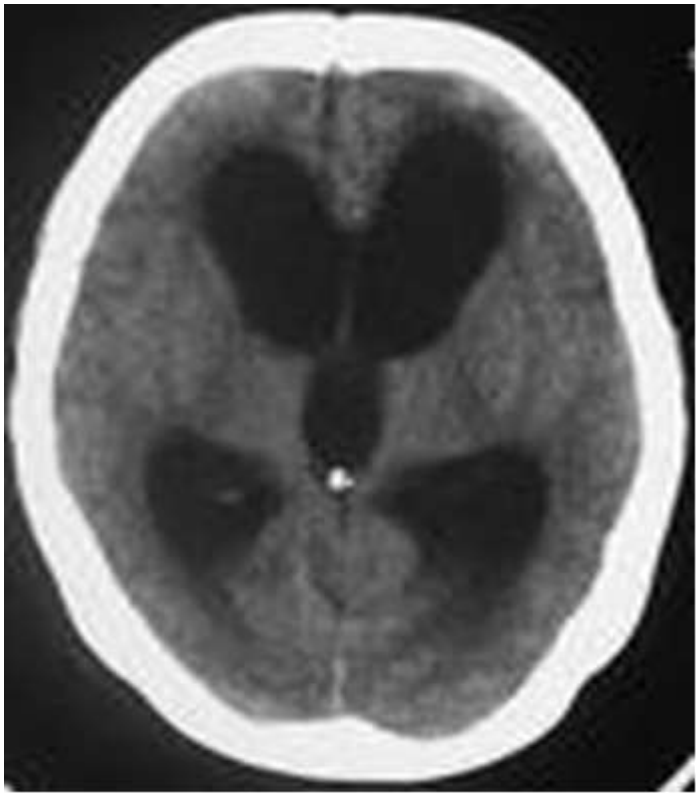

Figure 5. CT scan Brain showing hydrocehalus

CNS malformations:

- CNS malformations are frequently associated with hydrocephalus.and includes the following conditions:
- Arnold- Chiari malformation, which often accompanies a neural tube defect, portions of the brainstem and cerebellum are displaced caudally into the cervical spinal canal. This obstructs the flow of CSF in the posterior fossa, leading to hydrocephalus.
- Dandy-Walker malformation consists of a large posterior fossa cyst that is continuous with the fourth ventricle and defective development of the cerebellum, including partial or complete absence of the vermis. Hydrocephalus develops in 70 to 90 percent of patients with Dandy-Walker malformation, and is caused by atresia of the foramina of Luschka and Magendie.
- Vein of Galen malformation is a rare cause of hydrocephalus. Obstruction results from compression of the aqueduct of Sylvius by the markedly dilated and distorted vein of Galen. Presentation in the neonatal period typically includes intractable heart failure .
- • Syndromic forms Hydrocephalus can be part of syndromes associated with dysmorphic features and other congenital abnormalities . The most frequent cytogenetic disorders

associated with hydrocephalus are trisomies 13, 18, 9 and 9p, and triploidy. Rare autosomal recessive disorders include Walker-Warburg syndrome, which is also characterized by ocular anomalies, and hydrolethalus syndrome, in which micrognathia and postaxial polydactyly of the hands and preaxial polydactyly of the feet are associated.

- Intrauterine infections Intrauterine infections such as rubella, cytomegalovirus, toxoplasmosis, and syphilis can result in congenital hydrocephalus. The mechanism is inflammation of the ependymal lining of the ventricular system and the meninges in the subarachnoid space . This may lead to obstruction of CSF flow through the aqueduct or basal cisterns.

B. Acquired hydrocephalus:

Common causes of acquired hydrocephalus are CNS infections such as bacterial meningitis or viral infections including mumps, and tumors, especially posterior fossa medulloblastomas, astrocytomas, and ependymomas. These conditions interfere with the flow of CSF through the ventricular system.

Another important cause is hemorrhage into the subarachnoid space or, less commonly, into the ventricular system, by ruptured aneurysms, arteriovenous malformations, trauma, or systemic bleeding disorders. The hemorrhage induces an inflammatory response followed by fibrosis, obstructing the flow and/or absorption of CSF.

Posthemorrhagic hydrocephalus occurs in approximately 35 percent of preterm infants with intraventricular hemorrhage (IVH). It can be obstructive, communicating, or both, and can be transient or sustained, with slow or rapid progression.

Clinical Presentation of Hydrocephalus

The signs and symptoms of hydrocephalus result from increased intracranial pressure (ICP) and dilatation of the ventricles. The time of presentation depends upon the acuity of the process. If accumulation of excessive CSF is slow, allowing adjustments to occur, the patient may have a long period without symptoms. Rapid progression of ventricular dilatation typically results in early development of symptoms.

Symptoms of hydrocephalus are nonspecific and independent of the etiology . Headache is a prominent symptom. It is caused by distortion of the meninges and blood vessels. The pain often varies in intensity and location and may be intermittent or persistent. Headaches due to increased ICP often occur in the early morning and are associated with nausea and vomiting.

Affected patients often have changes in their personality and behavior. These include irritability, obstreperousness, indifference, and loss of interest. The mechanism of the behavior changes is uncertain, but related in part to increased ICP. As the hydrocephalus worsens, midbrain and brainstem dysfunction may result in lethargy and drowsiness. Increased ICP in the posterior fossa often leads to nausea, vomiting, and decreased appetite.

Physical examination: Physical findings are due to the effects of increased ICP. The following signs are often present.

- Distortions of the brainstem may result in changes in vital signs such as bradycardia, systemic hypertension, and altered respiratory rate.
- Excessive head growth may be noted on serial measurements of head circumference plotted on growth curves. However, significant dilatation of the ventricles can occur before head growth becomes abnormal.
- The anterior fontanelle may become full or distended.
- Young infants may develop frontal bossing, an abnormal skull contour in which the forehead becomes prominent.
- The scalp veins may appear dilated and prominent.
- Compression of the third or sixth cranial nerve may result in extraocular muscle pareses leading to diplopia.
- Pressure on the midbrain may result in impairment of upward gaze. This is known as the setting-sun sign because of the appearance of the sclera visible above the iris and this condition known as Parinaud syndrome .
- Fundoscopic examination may reveal papilledema.
- Stretching of the fibers from the motor cortex around the dilated ventricles may result in spasticity of the extremities, especially the legs.
- •Accelerated pubertal development, as well as disturbed growth and fluid and electrolyte homeostasis, may result from pressure of the dilated third ventricle on the hypothalamus

Diagnosis of Hydrocephalus

Hydrocephalus should be suspected in an infant whose head circumference is enlarged at birth. In some cases, the diagnosis is made by antenatal ultrasonography .Hydrocephalus should be considered in children with severe headache and other features suggesting increased ICP.

The diagnosis is confirmed by neuroimaging. In a newborn, ultrasonography is the preferred technique for the initial examination because it is portable and avoids ionizing radiation. In older infants and children, CT or MRI should be performed. Neuroimaging studies will also detect associated CNS malformations or tumors.

The site of obstructed CSF flow may be suggested by the pattern of ventricular dilatation. Stenosis of the aqueduct typically results in dilated lateral and third ventricles and a fourth ventricle of normal size.

A lumbar puncture (LP) should be performed and the CSF should be examined if an infection causing adhesive arachnoiditis or ependymitis is suspected. However, LP is contraindicated if the patient has evidence of a space-occupying lesion such as an intracranial tumor or a brain abscess, because of the risk of cerebral herniation.

Management of Hydrocephalus

The management of hydrocephalus can include medical therapy with dehydrating agents and steroids for patients in good grades and those with communicating hydrocephalus. However, surgery is required for patients with obstructive hydrocephalus and those in poor grades. Surgery can involve either a ventriculo-peritoneal shunt or endoscopic third ventriculostomy (ETV)3.

1. Shunt:

A mechanical shunt system is placed to drain the excessive accumulation of CSF. This involves placement of a catheter into one of the lateral ventricles, usually the right. The catheter is connected to a one-way valve system (usually placed beneath the scalp of the postauricular area) that opens when the pressure in the ventricle exceeds a certain value. The pressure decreases as fluid drains from the ventricles, resulting in closure of the valve until the pressure increases again

The distal end of the system is connected to a catheter that is placed in the right atrium of the heart or into the peritoneal cavity (ventriculoperitoneal, VP). This allows the CSF to bypass the site of mechanical or functional obstruction to absorption. CSF flows directly from the ventricles into the systemic circulation or to the peritoneum where it is absorbed. Early surgical procedure for mild/moderate hydrocephalus has a positive effect on the morbidity and mortality of hydrocephalus in childhood TBM [69]

Complications:

In general, complications of treated hydrocephalus are due to malfunction of the shunt. If the hydrocephalus is still active, symptoms recur and another drainage procedure is required Malfunction is due to infection or mechanical failure.

- **Infection**

Shunt infection is a common complication. Mostly occur in the first six months after shunt placement Infecting organisms are typically the patient's own skin flora, such as Staphylococcus epidermidis . Other organisms found less frequently include S. aureus, enteric bacteria, diphtheroids, and Streptococcus species.

Infection must be considered in a child with a shunt who develops persistent fever. Antibiotics should be started, but this treatment alone is usually not effective. In most cases, an infected shunt must be removed and an external ventricular drain temporarily placed. . Perioperative antibiotic prophylaxis may reduce the risk of infection.

- **Mechanical failure :**

Mechanical failure is an important problem, especially in the first year after shunt placement. The majority of first shunt failures result from obstruction at the ventricular catheter . This occurs because shunts typically overdrain, greatly reducing the size of the ventricles. This causes the catheter to lie against the ependyma and choroid plexus which block the holes at the end of the catheter. It has been observed

2. Endoscopic Third ventriculostomy:

Endoscopic third ventriculostomy (ETV), a procedure in which a perforation is made to connect the third ventricle to the subarachnoid space, has been used in the initial treatment of selected cases of obstructive hydrocephalus and as an alternative to shunt revision

Endoscopic third ventriculostomy is presented as a new application of a procedure accepted for other indications in the treatment of non-communicating hydrocephalus [70] The success of the procedure

depends upon the cause of hydrocephalus and previous complications . When successful, ETV provides a relatively low-cost and durable treatment for hydrocephalus.

Endoscopic third ventriculostomy is likely to fail in the presence of advanced clinical grade, extra-CNS tuberculosis, dense adhesions in prepontine cisterns, and an unidentifiable third ventricular floor anatomy [71] Patients who have complex hydrocephalus (combination of communicating and obstructive type) could result in failure of ETV in spite of a patent stoma [72].

The indications for ETV have increased in the last decade due to its safety it can be considered as a safe and long-lasting solution for hydrocephalus after chronic TBM. [73]

Tubercular meningitic hydrocephalus is difficult to treat endoscopically as compared with other forms of meningitic hydrocephalus Use of endoscopic third ventriculostomy in hydrocephalus of tubercular origin.and requires adequate expertise and experience, especially in acute cases.[74]

Endoscopic third ventriculostomy should be considered as the first surgical option for CSF diversion (that is, before shunt surgery) in patients with TBM hydrocephalus MR imaging is a highly effective noninvasive tool for the postoperative functional assessment of stomata. Patients who presented with a history of longer duration and those who were administered preoperative ATT for a longer period had a better outcome of endoscopic treatment. Outcome was poorer in patients who presented with higher stages of illness and in those in whom cisternal exudates were observed intraoperatively.[75]

The high Intracranial pressure (ICP) observed in a group of patients in the early postoperative days is probably related to the slow permeation of the subarachnoid spaces by the cerebrospinal fluid flowing out of the third ventriculostomy.

High postoperative ICP can account for persistent symptoms of intracranial hypertension and ventricular dilatation on computed tomographic scans after third ventriculostomy. A cycle of one to three lumbar punctures should always be performed in patients who remain symptomatic and who show increasing ventricular dilatation after ETV, before ETV is assumed to have failed and an extracranial cerebrospinal fluid shunt is implanted [76].

Cerebrospinal fluid (CSF) dynamics convert from a shunt-dependent state to a shunt-independent state within I week following ETV in patients with shunt-dependent noncommunicating hydrocephalus. Nonetheless, intraventricular pressure does not decrease quickly in certain cases. Cerebrospinal fluid absorptive capacity or CSF circulation through the subarachnoid space may show further improvement several months after ETV [77].

Clinical improvement is not well correlated with a decrease in ventricular size following ETV. Brain SPECT is a valuable tool for the follow-up of patients with hydrocephalus after ETV, particularly in cases in which MR imaging findings are not clear. There are subtle hormonal changes in patients with hydrocephalus that may improve following ETV [78].

Patients with shunt malfunction and patients with intraventricular mass lesions, showing a more pronounced trend to develop severe intracranial hypertension after ETV, should always be considered for postoperative ICP monitoring in order to detect and, eventually, treat any ICP rises which may occur. Unfortunately, it is still difficult to assign a predictive value to the different postoperative ICP patterns. [79]

Patients with obstructive hydrocephalus could benefit from ETV in case of their shunt malfunction and if carefully selected have about 70% probability to become shunt free. In formerly shunted patients, endoscopy has somewhat greater risk of serious complications; thus a wider experience is essential when offering them an ETV [80].

Prior CSF shunting in patients with obstructive hydrocephalus was associated with the decreased time to treatment failure following conversion to ETV. ETV may be less effective for the treatment of obstructive hydrocephalus in previously shunted patients.[81]

The risk of endoscopic third ventriculostomy (ETV) failure increases with intracerebral infection, likely because of obliteration of cerebrospinal fluid pathways. [82]

Assessment of third ventricular floor and lamina terminalis morphology is useful in predicting clinical success of ETV and in the follow-up in treated patients.[83]

ETV is an effective method of treating hydrocephalus in patients with normal ventricular anatomy and thin membrane at the third ventricular floor. Patients with thick membrane and tuberculous meningitis; and obscure anatomy have high failure rate.[84]

The water jet dissection technique in ETV can be useful in such cases to perform an initial perforation, especially in patients with a thick and opaque third ventricle floor and it minimises the Risk of Bleeding and Neurological Complications [85]. Endoscopic third venticulostomy (ETV) results in a high rate of good long-term outcome in patients with obstructive hydrocephalus. [86]

3. Medical therapy of Hydrocephalus:

Medical treatment includes the use of diuretics, fibrinolysis, and serial lumbar punctures. These procedures have significant complications and are less effective than surgical treatment.

Diuretics:

The diuretics furosemide and acetazolamide decrease CSF production. They have been used for short periods in slowly progressive hydrocephalus in patients too unstable for surgery. The administration of acetazolamide and furosemide did not decrease the risk for VP shunt or the combined outcome of shunt or death.

Fibrinolytic therapy:

Administration of fibrinolytic agents has been used in newborns with posthemorrhagic hydrocephalus in an attempt to prevent permanent obstruction to CSF flow. This treatment does not appear to reduce the need for shunt placement and may increase the risk of hemorrhage, but adequate trials are lacking [28]

Serial Lumbar Punctures

Repeated lumbar punctures have been used as a temporizing measure in preterm infants with posthemorrhagic hydrocephalus, although they do not appear to be effective. However, drainage of CSF was considered a reasonable treatment when evidence of increased intracranial pressure exists.

In cases of rapidly progressive hydrocephalus, a temporary ventricular drainage device may be needed until a permanent shunt can be placed or the hydrocephalus resolves spontaneously.

ORIGINAL STUDY

Objectives of Study

To determine the frequency of hydrocephalus in patients with tuberculous meningitis

Operational Definition

Tuberculous meningitis (TBM) is diagnosed majorly on the basis of CSF analysis.

Criteria for Tuberculous meningitis on CSF:

White cell count	> 5/mm3 (Predominantly Lymphocytes)
Protein	>46 mg/dl
Glucose	< 50mg/dl (or < 60% of serum glucose)

Radiological criteria for Hydrocephalus:

1) Size of both temporal horns is greater than 2 mm, clearly visible. In the absence of hydrocephalus, the temporal horns should be barely visible.
2) Ratio of the largest width of the frontal horns to maximal biparietal diameter (ie, Evans ratio) is greater than 30% in hydrocephalus.
3) Ballooning of frontal horns of lateral ventricles and third ventricle (ie, "Mickey mouse" ventricles) may indicate aqueductal obstruction.
4) Upward bowing of the corpus callosum on sagittal MRI suggests acute hydrocephalus

Material and Methods

Study Design: Cross sectional study.

Sample Size: 77 patients of TBM.

Calculated by using WHO (World Health Organization) sample size calculator, where; confidence level=95%, precision = 0.8, Using prevalence of 85% .3

Setting:

This study was carried out on patients of department of Neurology, Pakistan Institute of Medical Sciences (PIMS), Islamabad, affiliated with Quaid-e-Azam Post graduate Medical College (QPGMC), Islamabad. The Pakistan Institute of Medical Sciences is a 960-bedded hospital and considered to be one of the premier institutes in the country. It receives patients not only from the twin cities but also from upper Punjab, Khyber pakhtoon khuwah province and Azad Kashmir. The bed occupancy rate is more than 95% round the year. The department runs an OPD (out patient department) where 120-130 patients are seen daily with an admission rate of 6 – 12 / day. Patients are also admitted from emergency, which is continued around the clock seven days a week.

Duration of Study:

The defined time of study was 6 months after approval of synopsis. My synopsis was approved on 29th April, 2010. As I was on elective rotation that moment so I started my study on 15th September, 2010 and accomplished on 15th March, 2011.

Sample Selection:

Nonprobability consecutive sampling

Inclusion Criteria:

All patients diagnosed as case of TBM on the basis history and CSF examination, presenting in the department of neurology, PIMS, irrespective of their age and gender were included in this study. Main CSF findings suggestive of TBM were low glucose, raised proteins and lymphocytic leukocytosis.

Exclusion Criteria:

- Patients having space occupying lesions (SOL), other than tuberculoma
- Patients with congenital neurological anomalies
- Patients with cerebral degeneration/ atrophy

Data Collection Procedure

The study was conducted at the department of neurology, PIMS. After informed consent, all patients of Tuberculous meningitis (TBM) included as per criteria underwent brief history, taken by me as a researcher. Then computerized tomography (CT) brain was done which was reported by consultant radiologist, in department of radiology, PIMS. Later cerebrospinal fluid (CSF) was done and reported by senior pathologist in department of pathology, PIMS. Then proforma was filled by me in respects of brief history, clinical, radiological and CSF findings.

Data Analysis Procedure

Data was entered and analyzed using SPSS version 12. Mean and standard deviation were calculated for numerical variables (like age). Frequencies and percentages were calculated for qualitative variables (i, e gender, radiological and CSF findings). The results of study and their simple interpretation are as under:

Results

In this study sample size of 77 patients was taken, which comprised of 47 (61%) males and 30 (39%) females. Male to female ratio was 1.5:1.Age of the patients ranged 14-72 years (mean=27.3). Majority of the patients I received, belonged to age group of 21 to 40 years, means young people predominantly suffered from TBM. A significant number of my patients came from province Khyber pakhtoon khuwah.

We also looked for any other site affected by tuberculous infection other than meninges. Amongst other sites lungs were mainly involved, 15 (19.5%) patients showed pulmonary Koch's along with TBM. Other sites such as abdomen, genitourinary system, skin, lymph nodes and bones were also assessed for coexisting tuberculosis but they did not show involvement. In patients having pulmonary TB with TBM, 9 were female and 6 were male with a ratio of 1: 1.5 with female predominance. Such patients belonged to either adolescent or elderly age group.

We looked for presence of radiologic hydrocephalus in our patients, based on above mentioned criteria. Out of 77 patients 59 (76.6%) displayed hydrocephalus, amongst which 34 were male and 25 were female. The patients who had developed hydrocephalus at presentation were too young or too old.

Computerized tomography (CT) brain of the patients showed some other findings in addition to hydrocephalus which included tuberculomas and infarctions. Tuberculomas were seen in 9 (11.7%) patients which mainly belonged to adolescent and late adult age group, whereas 14 (18.2%) patients displayed infarctions which were majorly elderly in age. Both of these findings were predominantly seen in male gender.

Enrolled patients underwent cerebrospinal fluid (CSF) analysis after radiological assessment. Patients with above mentioned CSF criterion were labeled to have TBM. I looked for raised CSF proteins and corrected them by deduction of 1mg/dl of proteins for every 1000/mm3 RBCs in case of traumatic spinal tab. I found that majority of patients (62%) had CSF proteins in range of 46 – 200 mg/dl and very few (3.9%) had protein level above 1000mg/dl. Degree of raised CSF proteins had no specific association with age but it was mildly associated with gender. Higher degree of CSF proteins was displayed by male patients.

I also categorized CSF proteins as mild (46 – 200 mg/dl), moderate (201 – 500 mg/dl) and severe (>500 mg/dl) degrees. Presence of hydrocephalus was associated with degree of high CSF proteins. All the patients with severely raised proteins had hydrocephalus, whereas 70.5% of the patients with moderately and 77% of the patients with mildly raised proteins exhibited hydrocephalus. In fact, high CSF protein is the basic element involved in production of hydrocephalus.

Similarly, presence of radiological findings other than hydrocephalus was also compared with CSF protein content. Tuberculomas were mainly seen in patients with mildly high proteins whereas infarcts were predominantly seen in patients with severely raised proteins. Infarcts are usually produced by secondary vasculitis or endarteritis in case of TBM. Theory that high level of CSF proteins may play a significant role in endarteritis is obviously justified here.

We had the viewpoint that patients having tuberculosis at more than one site may show severe inflammation in meninges leading to severely elevated CSF proteins but idea was not justified practically. CSF proteins levels were also compared with presence of tuberculosis in other body organs. As mentioned above coexisting pulmonary tuberculosis was observed in 19.5% patients. These patients had mild to moderate degree of raised CSF proteins.

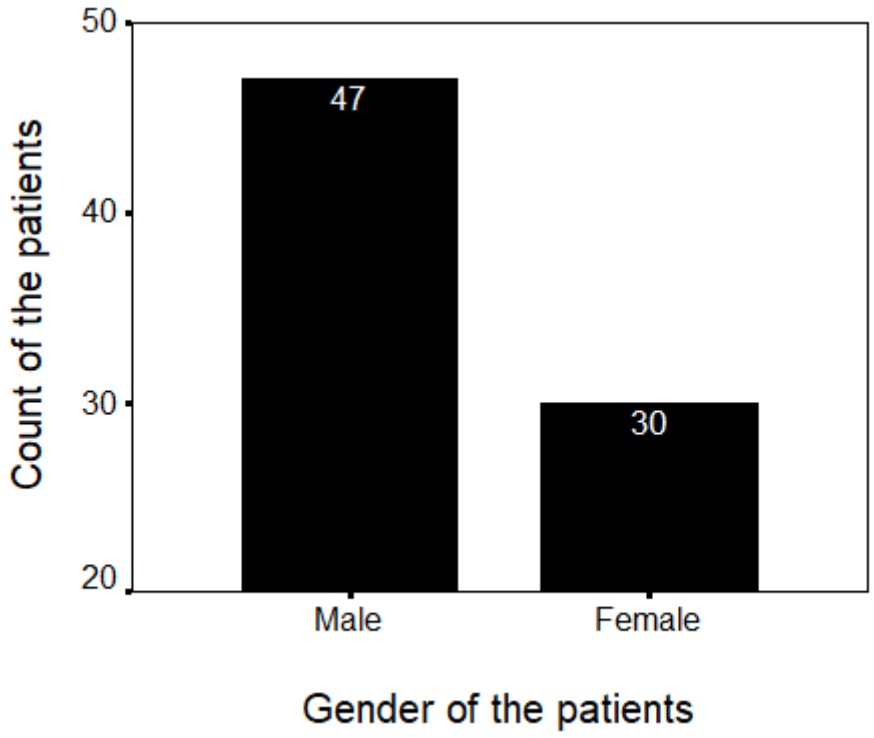

Figure 6: Graph showing gender distribution of the patients

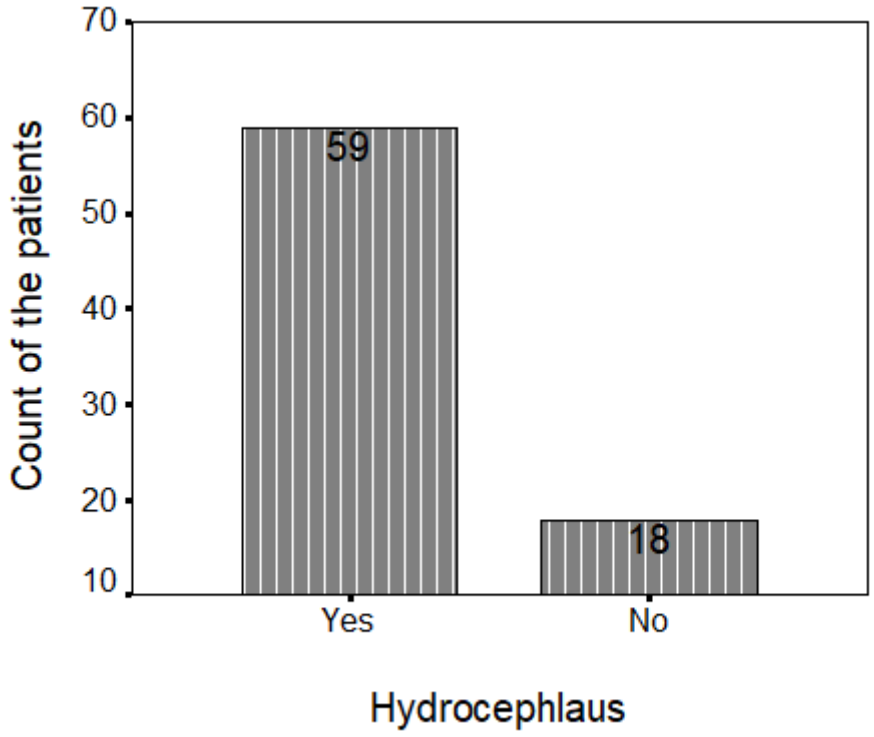

Figure 7. Graph showing presence of hydrocephalus with patient count

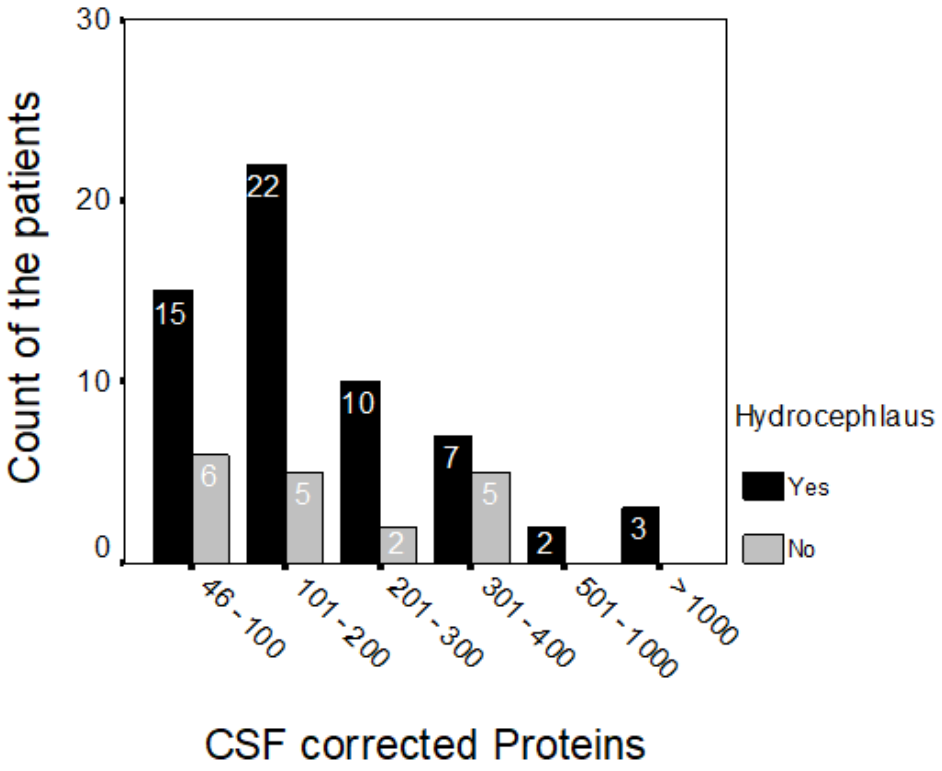

Figure 8. Graph showing corrected CSF proteins with presence of hydrocephalus

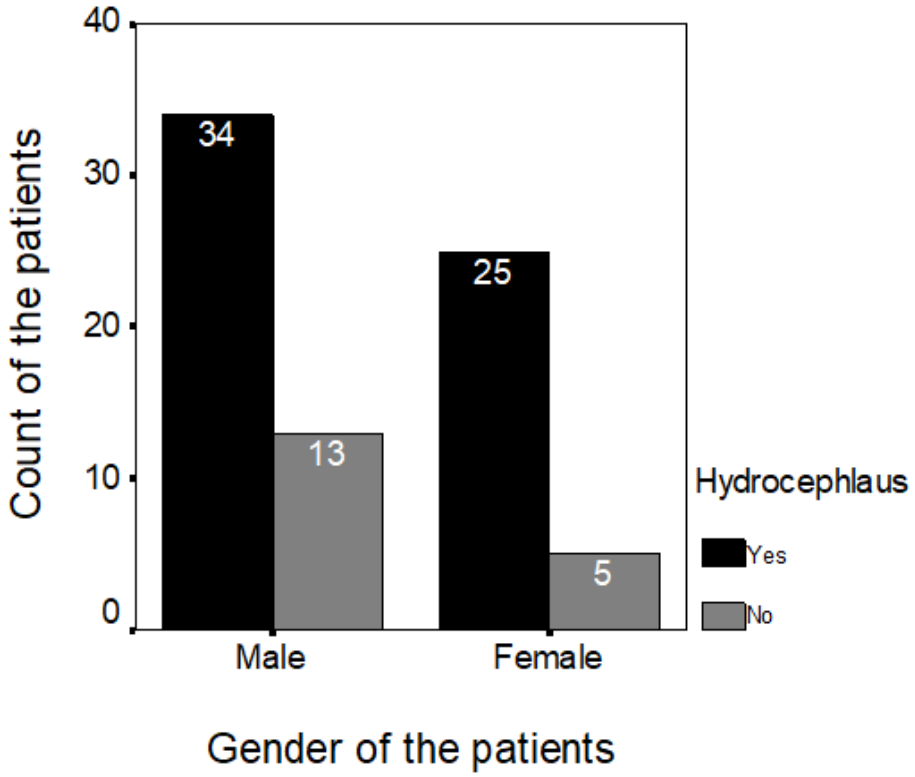

Figure 9: Graph showing gender distribution of patients with presence of hydrocephalus

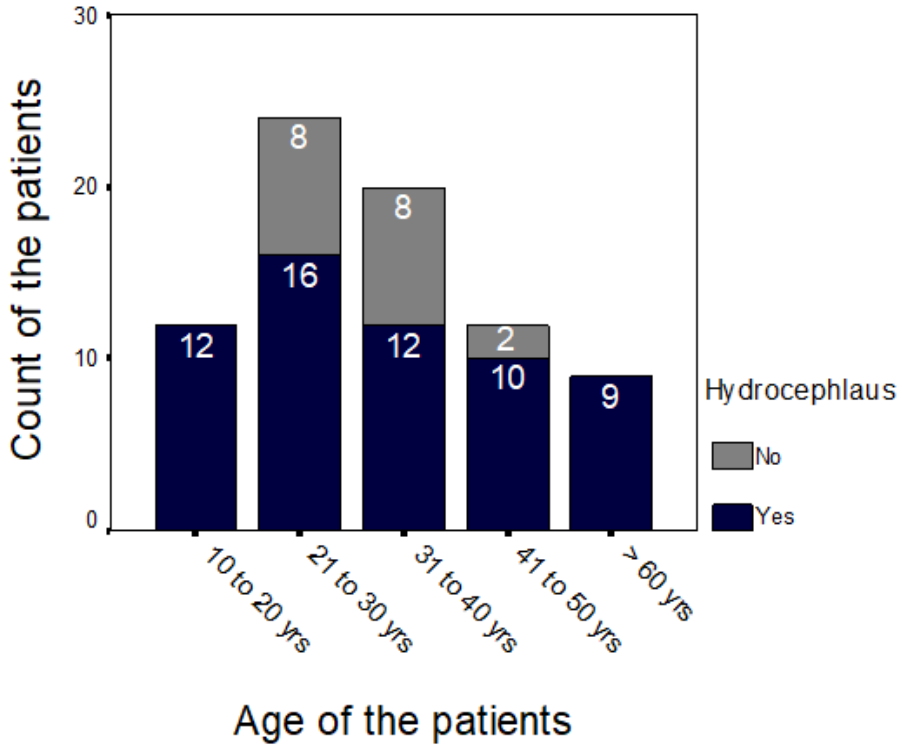

Figure 10. Graph showing age distribution of patients with presence of hydrocephalus

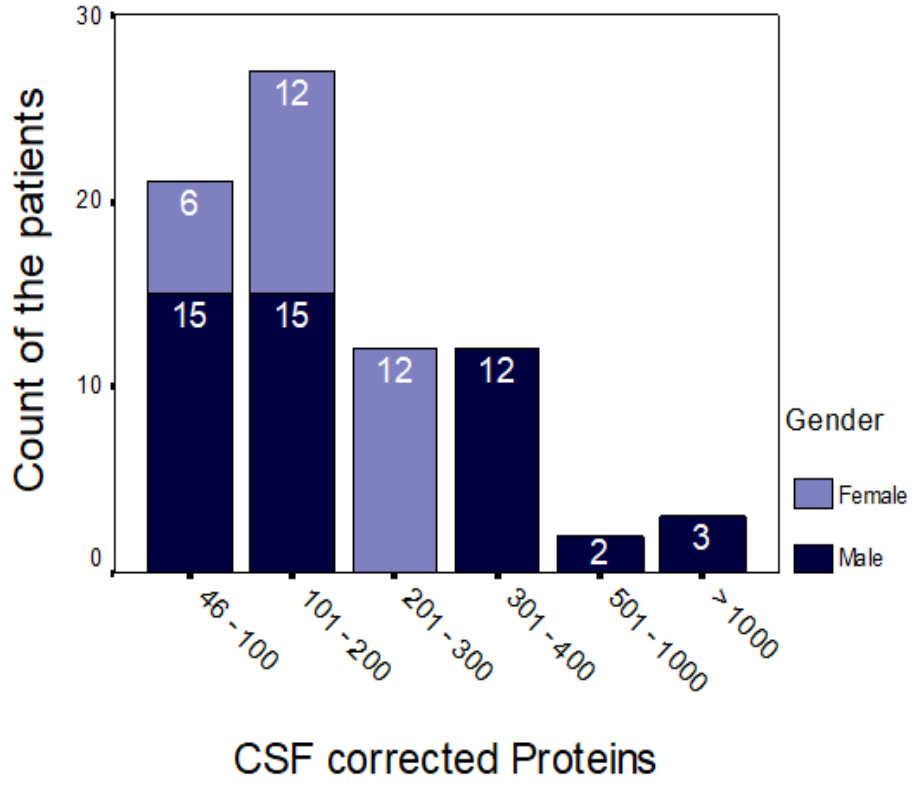

Figure 11: Graph showing corrected CSF proteins with gender distribution of the patients

CSF proteins (mg/dl)	Number of patients in age (in years) categories						
	10-20	21-30	31-40	41-50	51-60	>60	Total
46-100	9	9	3	0	0	0	21
101-200	3	6	9	3	0	6	27
201-300	0	0	3	9	0	0	12
301-400	0	6	3	0	0	3	12
401-500	0	0	0	0	0	0	0
501-1000	0	0	2	0	0	0	2
>1000	0	3	0	0	0	0	3
Total	12	24	20	12	0	9	77

Table 1. CSF proteins distributed in age categories

CSF proteins (mg/dl)	Number of patients with additional radiological findings			
	Infarction	Tuberculoma	No other	Total
46-100	3	6	12	21
101-200	3	0	24	27
201-300	3	3	6	12
301-400	3	0	9	12
401-500	0	0	0	0
501-1000	2	0	0	2
>1000	0	0	3	3
Total	14	9	54	77

Table 2: Showing additional radiological findings versus CSF proteins

Age (in years)	Number of patients with site of TB other than CNS			
	Pulmonary	Any other	No other	Total
10-20	3	0	9	12
21-30	3	0	21	24
31-40	0	0	20	20
41-50	3	0	9	12
51-60	0	0	0	0
>60	6	0	3	9
Total	15	0	62	77

Table 3: Number of patients having TB at site other than CNS plotted with age of patients.

CSF proteins (mg/dl)	Number of patients with site of TB other than CNS			
	Pulmonary	Any other	No other	Total
46-100	0	0	21	21
101-200	12	0	15	27
201-300	3	0	9	12
301-400	0	0	12	12
401-500	0	0	0	0
501-1000	0	0	2	2
>1000	0	0	3	3
Total	15	0	62	77

Table 4: Patients with extra CNS tuberculosis with their CSF proteins

Discussion

Tuberculosis can involve any organ system of the body. Tuberculosis of nervous system (NS) is not uncommon in our country. Tuberculous meningitis is a severe form of extrapulmonary tuberculosis. In countries with high burden of pulmonary tuberculosis, the incidence is expected to be proportionately high. Children are much more vulnerable. Human immunodeficiency virus-infected patients have a high incidence of tuberculous meningitis.17The hallmark pathological processes are meningeal inflammation, basal exudates, vasculitis and hydrocephalus. Headache, vomiting, meningeal signs, focal deficits, vision loss, cranial nerve palsies and raised intracranial pressure are dominant clinical features. Diagnosis is based on the characteristic clinical picture, neuroimaging abnormalities and cerebrospinal fluid changes. Cerebrospinal fluid smear examination, mycobacterial culture or polymerase chain reaction is mandatory for bacteriological confirmation. In the nervous system tubercle bacilli can cause tuberculous meningitis, abscess, tuberculoma in brain & spinal cord. Untreated Central Nervous System (CNS) tuberculosis is devastating. Early diagnosis & prompt treatment of TB of nervous system is essential to avoid morbidity & mortality. Tubercle bacilli causes chronic caseating granulomatous lesion. Tuberculoma may present with headache, seizure and focal deficit. In the spinal cord tuberculoma or tubercular abscess may result in paraparesis or quadri-paresis. For diagnosis of nervous system tuberculosis CSF analysis and neuroimaging are important. More research is urgently needed to better understand the pathogenesis of disease and to improve its clinical management and outcome. A major stumbling block is the absence of standardised diagnostic criteria. The different case definitions used in various studies makes comparison of research findings difficult, prevents the best use of existing data, and limits the management of disease.

In my study 19.5% of TBM patients had additional pulmonary tuberculosis, whereas in another study 46% patients showed radiographic evidence of chest TB along with TBM. [21]

In my study hydrocephalus was found in 76.6% patients of TBM, whereas according to an Indian study hydrocephalus is one of the commonest complications of tuberculous meningitis (TBM) occurring in up to 85% of children with this disease. 3It is more severe in children than in adults. It could be either of the communicating type or the obstructive type with the former being more frequently seen. Another study done at Vietnam showed hydrocephalus seen in 77% and tuberculomas in 74% patients .58 According to another study done at Lucknow, India out of total 16 patients hydrocephalus was present in 9, infarction in 7 and tuberculoma in 5 patients.87A study done in New Zealand showed complications of TBM include hyponatraemia 49%, hydrocephalus 42%, stroke 33%, cranial nerve

palsies 29%, epileptic seizures 28%, diabetes insipidus 6%, tuberculoma 3%, myeloradiculopathy 3% and hypothalamic syndrome 3%.[88]

Early follow-up CT is useful in making a diagnosis of TBM by demonstrating features that were not present initially and by demonstrating more sensitive, obvious or additional features of TBM. In addition, follow-up CT is valuable as a prognostic indicator as it demonstrates additional infarcts which may have developed or become more visible since the initial study. Lastly, follow-up CT has therapeutic value in demonstrating hydrocephalus, which may develop over time and may require drainage. So another study conducted at Cape Town, South Africa advised routine follow-up CT in patients with suspected TBM within the first week of initial CT and optionally after 1 month.43Hydrocephalus had strong association with severe neurological deficit and seizure with death in both the groups.[62]

Other radiologic findings were also seen in my study, which included infarction 18.2% and tuberculomas in 11.7% patients. Stroke due to infarction in tuberculous meningitis occurs in 15-57% of patients especially in advance stage and severe illness.[25]

In another study conducted in South Africa showed radiological brainstem abnormalities were identified in 14 out of 30 children and these were associated with poor outcome.89 In a study conducted at Hong Kong showed infarction in 30% patients of TBM, 23% were symptomatic and in 8% patients they were silent. Out of these 58% had large artery infarcts with or without lacunar infarcts and 67%) had only lacunar infarcts.24An Indian study concluded that infarction occurred in 30% of cases with tuberculous meningitis. Advanced stage of tuberculous meningitis, basal exudates, optochiasmatic arachnoiditis and vision impairment were significant predictors of stroke.[61]

In comparison to 11.7% of my study tuberculomas occurred in approximately 39% of the patients with TBM in an Indian study.30 Similarly another Indian study showed tuberculomas in 13 out of 31 patients on initial CT scan.[90]

I compared CSF proteins with presence of hydrocephalus and found that higher the range of CSF proteins more was incidence of hydrocephalus. This can be due to increased inflammatory exudates, more arachniditis leading to obstruction of CSF flow channels causing hydrocephalus.

Hydrocephalus can be treated with Ventriculo-peritoneal shunting and Endoscopic third ventriculostomy. In an Indian study Ten out of the 71 patients (14%) with obstructive hydrocephalus due to TBM, who underwent an Endoscopic third ventricuostomy (ETV) had a complex hydrocephalus, which was the major (66.7%) cause for failure of ETV.72 Improving methods to detect

the exact type of hydrocephalus pre-operatively could increase success rate of ETV and avoid an unnecessary operative procedure. Moreover, Dexamethasone may affect outcome from tuberculous meningitis by reducing hydrocephalus and preventing infarction.[58]

Conclusion

Tuberculosis is a common disease in our community and it can be most dangerous when it involves central nervous system. Hydrocephalus is one of the radiologic manifestations of TBM, which is usually seen in patients with high CSF protein content irrespective of their gender and age.

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