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Frequency of Obstructive Hydrocephalus in Children with Tuberculous Meningitis

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Abstract

Introduction: Tuberculous meningitis is the Mycobacterium tuberculosis infection of the meninges around the brain. It is a very critical disease in terms of fatal outcomes and permanent sequelae, requiring prompt diagnosis and urgent treatment. Despite the great advances in all the fields of medical science, tuberculous meningitis still remains amongst the greatest public health challenges in developing countries like Pakistan. Tuberculosis is among the top 10 causes of death worldwide. Hydrocephalus is one of the most common complications of tuberculous meningitis.

Objective: To determine the frequency of obstructive hydrocephalus in tuberculous meningitis.

Study Setting: The study was carried out at the Medical, Neurology and, Neurosurgery Departments of Children Hospital, Lahore.

Duration of Study: November 30, 2020, to May 30, 2021

Study Design: Cross-Sectional Study

Subjects & Methods: A total of 278 Patients with Tuberculous meningitis fulfilling inclusion criteria were selected for the study. Patients were labeled as having obstructive hydrocephalus as per the report of their MRI brain done by a single consultant radiologist to avoid bias. Tuberculous meningitis and obstructive hydrocephalus were managed as per hospital protocol. Statistical package for the social sciences (SPSS) v25.0 software was used to analyze the collected data. Data were stratified for age, gender, and duration of TBM. Post-stratification, a Chi-square test was applied. A p-value ≤0.05 was considered significant.

Result: In this study, 278 patients who had Tuberculous meningitis fulfilling the selection criteria were included. Among these patients, 159(57.2%) were males and 119(42.8%) were females. The mean age of the patients was 6.2±2.3 years with 6 months and 12 years as minimum and maximum ages. Among these patients, 61(21.9%) patients had obstructive hydrocephalus.

Conclusion: Obstructive Hydrocephalus is an important and deadly complication of tuberculous meningitis and even its low presence cannot be ignored. Management and assessment of Obstructive Hydrocephalus in children with Tuberculous meningitis should be carefully monitored.

Keywords: Obstructive Hydrocephalus; Tuberculous Meningitis

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Introduction

Tuberculous meningitis is the Mycobacterium tuberculosis infection of the meninges around the brain. It is a very critical disease in terms of fatal outcomes and permanent sequelae, requiring prompt diagnosis and urgent treatment. Despite the great advances in all the fields of medical science, tuberculous meningitis remains amongst the greatest public health challenges in developing countries like Pakistan. Tuberculosis is among the top 10 causes of death worldwide [1]. Currently, more than 2 billion people (one-third of the world's population) are infected with tuberculosis, of which approximately 10% will develop clinical disease. Tuberculous meningitis is a very common disease in young children killing or disabling almost half of the affected [2]. Children are more vulnerable to developing it because of their poor immune response to contain the organism within the lungs. Hydrocephalus is one of the most common complications of tuberculous meningitis [3]. A study in Pakistan showed that 58% of tuberculous meningitis patients developed hydrocephalus [4] .It is almost always present in patients who have had the disease for four to six weeks [5]. It could be either the communicating or the obstructive type with the former being more frequently seen. Surgery is required for patients with obstructive hydrocephalus. In patients with evidence of obstructive hydrocephalus and neurological deterioration who are undergoing treatment for tuberculous meningitis, placement of a ventriculoperitoneal shunt should not be delayed. Studies suggest that prompt shunting improves outcomes, particularly in patients presenting with minimal neurologic deficits [6]. In a study done in South, Africa hydrocephalus was communicating in 79%, and non-communicating in 7% [7]. A study done in Malaysia showed hydrocephalus in tuberculous meningitis to be 62% of which 73% had obstructive hydrocephalus and 27% had to communicate hydrocephalus [8]. Despite the high prevalence of tuberculous meningitis in Pakistan very little research has been done on this topic. This study was conceived with the idea to highlight the frequency of obstructive hydrocephalus in our population and register the changes in frequency in recent times.

Review of Literature

Hydrocephalus is a disorder in which an excessive amount of cerebrospinal fluid (CSF) accumulates within the cerebral ventricles and/or subarachnoid spaces, resulting in ventricular dilation and increased intracranial pressure (ICP) [9].

Terminology

Obstructive Hydrocephalus

Obstructive hydrocephalus (also called non-communicating hydrocephalus) refers to excessive accumulation of cerebrospinal fluid (CSF) due to structural blockage of CSF flow within the ventricular system. This is the most common form of hydrocephalus in children and is almost always associated with increased intracranial pressure (ICP).

Communicating hydrocephalus

Communicating hydrocephalus refers to CSF accumulation due to impaired absorption that occurs in the subarachnoid spaces. Rarely, CSF accumulates because of excessive production. Communicating hydrocephalus is also typically associated with increased ICP. There is some overlap in these categories. Many causes of hydrocephalus have both obstructive and absorptive components, and the absorptive component of the hydrocephalus may change over time.

Normal pressure hydrocephalus

In normal pressure hydrocephalus (NPH), the cerebral ventricles are pathologically enlarged, but the ICP is not elevated. NPH is most often seen in adults over the age of 60 years.

Ventriculomegaly

Ventriculomegaly is a general term used to describe enlargement of the ventricles as seen in neuroimaging. Ventriculomegaly is a common finding in all forms of hydrocephalus. It is also seen in other conditions that are not associated with hydrocephalus (eg, brain atrophy). The forms of hydrocephalus described above are distinct from two radiographic findings that include the same word

Hydrocephalus ex-vacuo

This term refers to the enlargement of the CSF spaces caused by the reduced volume of brain tissue due to atrophy or malformation. It is not accompanied by increased ICP.

Benign external hydrocephalus

Benign external hydrocephalus (also called "benign enlargement of the subarachnoid space" or "benign extra-axial fluid of infancy") is a relatively common cause of macrocephaly in infancy and frequently occurs in other family members [10]. As the name implies, the condition is self-limited, and affected infants usually do not require any intervention.

Epidemiology

The reported prevalence of congenital and infantile hydrocephalus in the United States and Europe ranges from 0.5 to 0.8 per 1000 live and stillbirths [11-12]. Myelomeningocele is the most common cause of congenital hydrocephalus and accounts for approximately 15 to 25 percent of these cases [13-14]. The most common cause of acquired hydrocephalus in infants is hemorrhage, usually as a consequence of prematurity [15]. Other common causes of acquired hydrocephalus include tumors and infections. Factors associated with an increased risk of infantile hydrocephalus include [14].

a. Birth weight <1500 g
b. Prematurity (gestational age ≤30 weeks)
c. Low socioeconomic status
d. Male sex
e. Race/ethnicity (the risk is decreased in Asians)

There is substantial familial aggregation for congenital hydrocephalus. In a population-based study of congenital hydrocephalus (not including cases associated with neural tube

defects), the recurrence risk ratios for same-sex twins, first-degree relatives, and second-degree relatives were 34.8, 6.2, and 2.2, respectively [16].

Physiology

Cerebrospinal fluid (CSF) is produced primarily by the choroid plexus. It circulates through the ventricular system, then through the subarachnoid space to the arachnoid villi, and from there it is absorbed into the systemic blood circulation. The flow of CSF is primarily cephalad.

CSF production

Cerebrospinal fluid (CSF) is produced primarily by the choroid plexus, which is responsible for 60 to 80 percent of CSF production. The choroid plexus tissue is located in each cerebral ventricle and consists of villous folds lined by epithelium with a central core of highly vascularized connective tissue. The choroidal epithelial cells produce CSF using active transport dependent upon carbonic anhydrase, which can be blocked by acetazolamide (Diamox), a carbonic anhydrase inhibitor. In addition to the active secretion, there is a diffusion component that is not blocked by acetazolamide. The remainder of the CSF is produced by cerebral tissue, which secretes CSF directly into the extracellular space. This fluid flows through the ependymal layer into the cerebral ventricles or the spinal central canal. CSF production rates are constant in physiologic conditions unless extremely high levels of intracranial pressure (ICP) are reached. Thus, absorption of CSF generally matches the rate of production to accommodate the volume of CSF being formed each day. In adults, the production rate of CSF is approximately 20 mL/hour, which results in complete turnover of the CSF three or four times per day. In newborns and young children, the CSF production rate is proportional to the size of the brain. Estimates of CSF production rates in infants and children are derived from measurements of the hourly output of the CSF from external ventricular drains. These studies suggest that CSF output increases logarithmically with age and body weight, ranging from 0.1 to 26.5 mL/hour [17]. Output increases rapidly in infancy; by the age of two years, the output is approximately two-thirds of adult levels. The total volume of CSF in the newborn is approximately 50 mL, compared with 125 to 150 mL in a healthy adult. In adults, approximately 25 percent of the CSF is within the ventricular system.

CSF circulation

The cerebrospinal fluid (CSF) originating in the choroid plexus and cerebral tissue circulates through the ventricular system into the subarachnoid space. The ventricular system is comprised of a pair of lateral ventricles, each of which connects to the midline third ventricle through an interventricular foramen (of Monro). There are no direct connections between two lateral ventricles because they are separated by a membrane (the septum pellucidum). The third ventricle is connected to a midline fourth ventricle by the cerebral aqueduct (of Sylvius). The CSF exits from the fourth ventricle into the subarachnoid space via three foramina: the paired lateral foramina of Luschka and a midline foramen of Magendie. Focally enlarged areas of subarachnoid spaces known as cisterns are present at the base of the brain. 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.

CSF Absorption

Cerebrospinal fluid (CSF) is absorbed into the systemic venous circulation primarily across the arachnoid villi into the venous channels of the major sinuses. The arachnoid villi consist of a cluster of cells that project from the subarachnoid space to the sinus lumen; these are covered by a layer of endothelium with tight junctions that are continuous with the inner layer of the sinuses. This assembly acts as a one-way valve, allowing passive absorption of CSF down a pressure gradient; if the CSF pressure is less than the venous pressure, the arachnoid villi close and do not allow blood to pass into the ventricular system. The rate of absorption is relatively linear over the physiologic range. Some CSF absorption also occurs across the ependymal lining of the ventricles and the choroid plexus, as well as from the spinal subarachnoid space to the perineural spaces. In addition to these well-described transport mechanisms, other pathways that may be involved in the movement of CSF include perivascular pathways and dura-associated lymphatic vessels. However, the role of these lymphatic pathways has not been elucidated.

Pathogenesis

Hydrocephalus results from an imbalance between the intracranial cerebrospinal fluid (CSF) inflow and outflow. It is caused by obstruction of CSF circulation, inadequate absorption of CSF, or (rarely) overproduction of the CSF. Regardless of the cause, the excessive volume of CSF causes increased ventricular pressure and leads to ventricular dilatation. It is increasingly recognized that many cases of hydrocephalus have both obstructive and absorptive components [18]. This accounts for the variable response to the third ventriculostomy for cases of hydrocephalus previously presumed to be purely obstructive. Moreover, the absorptive component of the hydrocephalus and the response to treatment may change over time.

Obstruction

The most common mechanism of hydrocephalus is an anatomic or functional obstruction to CSF flow (known as obstructive or non-communicating hydrocephalus). The obstruction occurs at the foramen of Monro, at the aqueduct of Sylvius, or the fourth ventricle and its outlets. The dilatation of the ventricular system occurs proximal to the obstruction. The ventricle just proximal to the obstruction usually dilates most prominently. Examples include:

a. Obstruction of the aqueduct of Sylvius (aqueduct stenosis) causes dilation of the lateral and third ventricles, while the size of the fourth ventricle remains relatively normal. This is a very common cause of hydrocephalus in infants and children.

b. Obstruction at the body of the lateral ventricle causes dilation of the distal temporal horn and atrium.

c. Obstruction of one foramen of Monro causes dilatation of the lateral ventricle on that side.

d. Obstruction of outflow from the fourth ventricle causes dilation of all four ventricles.

Impaired absorption

Less commonly, hydrocephalus is caused by impaired absorption of CSF, known as communicating hydrocephalus. This is typically due to inflammation of the subarachnoid villi but also may be caused by impaired CSF absorption or increased pressure in the venous sinuses. The radiographic hallmark of communicating hydrocephalus is the dilation of the entire ventricular system, including the fourth ventricle. Impaired CSF absorption also can occur when cranial venous sinus pressure is elevated.

Excessive production

Excessive production of CSF is a rare cause of hydrocephalus. This condition may occur with a functional choroid plexus papilloma. It leads to enlargement of the entire ventricular system and of the subarachnoid spaces, with a radiographic appearance that is similar to communicating hydrocephalus from other causes.

Pathophysiology

The pathophysiology of hydrocephalus depends upon the underlying cause, how quickly the condition develops, and the presence or absence of compensatory mechanisms:

a. Hydrocephalus that begins in infancy before fusion of the cranial sutures, if untreated, typically results in marked enlargement of the head and less compromise of brain tissue, compared with hydrocephalus that develops acutely. This is because the skull expands, partially relieving the intracranial pressure (ICP).In addition, the force of the ICP is distributed over the greater surface area of an enlarged ventricular system, so there is less pressure on the brain parenchyma compared with hydrocephalus that develops in a ventricular system that is not previously enlarged.

b. If hydrocephalus occurs acutely or occurs after fusion of the cranial sutures, the head does not enlarge. This results in significantly increased ICP and more rapid destruction of brain tissue. The progression of ventricular dilatation is usually uneven. The frontal and occipital horns typically enlarge first and to the greatest extent. Their progressive enlargement disrupts the ependymal lining of the ventricles, allowing the cerebrospinal fluid (CSF) to move directly into the brain tissue. This reduces CSF pressure but also leads to edema of the subependymal areas and progressive involvement of the white matter.

As the hydrocephalus progresses, edema and ischemia develop in the periventricular brain tissue, leading to atrophy of the white matter. The gyri become flattened, and the sulci become compressed against the cranium, obliterating the subarachnoid space over the hemispheres. The width of the cerebral mantle may be substantially reduced; gray matter is better preserved than white matter, even in advanced stages. The vascular system is compressed, and the venous pressure in the dural sinuses increases.

Etiology

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

Congenital

Congenital hydrocephalus can result from central nervous system (CNS) malformations (which include non-syndromic and syndromic disorders), infection, intraventricular hemorrhage, genetic defects, trauma, and teratogens [19]. A rare cause of hydrocephalus is obstruction caused by a congenital CNS tumor, especially if located near the midline. The disorders can be grouped according to the primary pathogenic mechanism (obstructive versus absorptive).

Neural tube defects

The majority of patients with myelomeningocele have hydrocephalus. In this setting, hydrocephalus is caused by the Chiari II malformation which obstructs the outflow of CSF from the fourth ventricle and/or flows through the posterior fossa. In addition, there is often associated with aqueduct stenosis. Hydrocephalus associated with myelomeningocele tends to have both an obstructive component and a communicating component [18]. Encephalocele is another relatively common neural tube defect, in which the brain and/or meninges herniate through a defect in the skull. Up to 50 percent of individuals with occipital encephalocele have associated hydrocephalus.

Isolated hydrocephalus

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

An association with maternal antidepressant use was suggested by a large registry study (rate ratio 2.52, 95% CI 1.47-4.29) [20]. However, other large registry studies and meta-analyses have not found an association.

X-linked hydrocephalus

The most common genetic form of congenital hydrocephalus is X-linked hydrocephalus due to stenosis of the aqueduct of Sylvius (aqueduct stenosis), which accounts for approximately 5 percent of cases of congenital hydrocephalus [19]. Approximately 50 percent of affected boys have adducted thumbs, which helps make the diagnosis. Some have other CNS abnormalities such as agenesis (or dysgenesis) of the corpus callosum, small brainstem, pachygyria, polymicrogyria, or absence of the pyramidal tract [21]. This disorder is due to mutations in the gene encoding L1, a neuronal cell adhesion molecule that belongs to the immunoglobulin superfamily and that is essential in neurodevelopment [22]. The gene for L1 has been mapped to Xq28. Mutations in L1 also result in other conditions, known as the L1 spectrum, that are characterized by neurologic abnormalities and by mental retardation. These include MASA spectrum (Mental retardation, Aphasia, Shuffling gait, Adducted thumbs), X-linked spastic paraplegia type 1, and X-linked agenesis of the corpus callosum.

CNS malformations

Central nervous system (CNS) malformations are frequently associated with hydrocephalus.

a. In the Chiari malformations, which often accompany 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. The Chiari II malformation seen in spina bifida is acquired and is accompanied by other features on magnetic resonance imaging (MRI), such as agenesis of the corpus callosum, low lying torcular herophili, tectal breaking, medullary kinking, and heterotopias.

b. The Dandy-Walker malformation consists of a large posterior fossa cyst that is continuous with the fourth ventricle and defective development of the cerebellum, including a 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.

Dandy-Walker malformation is a heterogeneous disorder. Some patients have a syndromic form with associated congenital anomalies including dysgenesis of the corpus callosum, orofacial deformities, and congenital abnormalities of the heart, genitourinary, and gastrointestinal systems [23]. There is a wide range of neurodevelopmental outcomes, which depend upon the effectiveness of the management of hydrocephalus as well as the associated CNS abnormalities.

A vein of Galen malformation is a rare cause of hydrocephalus. The hydrocephalus in these patients is primarily caused by arterial pressure in the venous system rather than by compression of the aqueduct. Presentation in the neonatal period typically includes intractable heart failure [24].

Syndromic forms

Hydrocephalus can be part of syndromes associated with dysmorphic features and with other congenital abnormalities [19]. A complete list of syndromes associated with hydrocephalus is too numerous to include here. The most frequent cytogenetic disorderles include trisomies 13, 18, 9, and 9p, as well as triploidy [19]. Rare autosomal recessive disorders include Walker-Warburg syndrome, which is also characterized by ocular anomalies, and hydrolethalus syndrome, which is associated with micrognathia, postaxial polydactyly of the hands, and preaxial polydactyly of the feet.

Intrauterine infection

Intrauterine infections such as rubella, cytomegalovirus, toxoplasmosis, lymphocytic choriomeningitis (LCM), syphilis, and Zika virus can result in congenital hydrocephalus. The mechanism is inflammation of the ependymal lining of the ventricular system and the meninges in the subarachnoid space [19]. This may lead to impaired absorption of CSF and/or obstruction of CSF flow through the aqueduct or basal cisterns [18].

Choroid Plexus Papilloma or Carcinoma

A papilloma or carcinoma of the choroid plexus may cause communicating hydrocephalus because of increased CSF secretion. This disorder usually can be identified by MRI.

Acquired hydrocephalus

Post-Hemorrhagic Hydrocephalus

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. The main mechanism for hydrocephalus is impaired absorption of CSF (communicating hydrocephalus), although some obstruction to CSF flow also may occur. Post-hemorrhagic hydrocephalus occurs commonly in preterm infants with intraventricular hemorrhage (IVH), particularly following grade III IVH or periventricular hemorrhagic infarction. It can be obstructive, communicating, or both and can be transient or sustained, with slow or rapid progression.

CNS tumors

Central nervous system (CNS) tumors (particularly posterior fossa medulloblastomas, astrocytomas, and ependymomas) are a common cause of acquired hydrocephalus in children. The mechanism usually involves obstruction of CSF flow by the tumor; however, impaired CSF absorption may also occur [18]. Hydrocephalus may be seen at the initial presentation or may occur as a later complication.

CNS infections

Hydrocephalus may occur as a consequence of central nervous system (CNS) infections (eg, bacterial meningitis or viral infections such as mumps). The mechanism can involve obstruction of CSF flow and/or impaired CSF absorption [18].

Low-Pressure Hydrocephalus

This is an uncommon entity in children and is extremely challenging to manage. It is diagnosed when neurologic improvement is attained by external ventricular drainage. Patients usually have symptomatic ventriculomegaly and very low intracranial pressure. This condition may result from tumors, chronic hydrocephalus, subarachnoid hemorrhage, and infections. Management is with low-pressure shunts [25].

Management

Overview

Timely referral to a pediatric neurosurgeon is important to ensure appropriate management of children with hydrocephalus. In addition, referral to a pediatric neurologist is often warranted, particularly if there are associated conditions such as seizures and/or developmental delays Most cases of hydrocephalus are progressive, meaning that neurologic deterioration will occur if the hydrocephalus is not effectively and continuously treated. For most patients, the most effective treatment is surgical drainage, using a shunt or third ventriculostomy. Rare exceptions include

cases of hydrocephalus caused by a vein of Galen malformation, embolization of the malformation may be more appropriate than surgical drainage [26]. Rarely, hydrocephalus is not progressive because alternate pathways of cerebrospinal fluid (CSF) absorption develop or because normal mechanisms for CSF handling become re-established. This is known as "arrested hydrocephalus." In this case, shunting is unnecessary.

Management Approach

The need for and timing of surgical intervention in patients with hydrocephalus is determined by the severity of symptoms and the neuroimaging findings:

Acute Rapidly Progressive Hydrocephalus

Patients with acute rapidly progressive hydrocephalus require urgent surgical intervention, typically with a CSF shunt or endoscopic third ventriculostomy (ETV). Temporizing measures may be needed for patients with a life-threatening presentation (eg, signs of herniation) and those who are too unstable to undergo surgery. In these circumstances, management often consists of the placement of a temporary external ventricular drain (EVD). Diuretic therapy is a less effective option. Serial lumbar punctures are not recommended. If the hydrocephalus is due to a structural cause such as a resectable brain tumor, the appropriate intervention consists of the removal of the tumor, often with intraoperative EVD placement. If the tumor is not resectable, then a CSF shunt or ETV can be performed to address the hydrocephalus.

Ventriculostomy

In cases of rapidly progressive hydrocephalus, a temporary EVD may be needed until a permanent shunt can be placed or until the hydrocephalus resolves spontaneously [27]. EVD placement can be lifesaving in this setting. An EVD is a small catheter inserted through the skull usually into the lateral ventricle, which is typically connected to a closed collecting device to allow for drainage of CSF. The EVD can also be connected to a transducer to measure ICP. The major complications associated with EVD are catheter occlusion and infection.

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.

Serial lumbar punctures

In preterm infants with post-hemorrhagic hydrocephalus, repeated lumbar punctures are sometimes used as a temporizing measure before placement of a more definitive CSF diverting device. However, the routine use of serial LPs as a preventive measure in neonates with intraventricular hemorrhage does not appear to be effective and is not recommended [28].

Symptomatic and high-risk patients

Surgical intervention (with CSF shunt or ETV) is generally indicated in patients with hydrocephalus if any of the following are present:

a. Symptoms (eg, headaches, vomiting, irritability, developmental delays, focal neurologic deficits, papilledema)

b. Progression of ventriculomegaly on neuroimaging

c. Clear obstruction of the CSF pathway evident on neuroimaging

Asymptomatic and Low-Risk Patients

Asymptomatic patients who lack findings suggestive of elevated ICP (eg, papilledema, bulging fontanel), are achieving expected developmental milestones, and do not have severe ventriculomegaly or obvious obstruction of the CSF pathway on neuroimaging can be managed with watchful waiting.

Young infants are followed with serial head measurements, monthly or bi-monthly head ultrasounds, and assessment of gross motor skills. Ultrasound is generally preferred for this monitoring because it is time-efficient, inexpensive, and doesn't require sedation.

If there is an ongoing clinical concern after the anterior fontanelle closes, magnetic resonance imaging (MRI) is the preferred modality for follow-up neuroimaging. Limited imaging with ultra-fast MRI can also be used as an alternative to ultrasonography in young infants. If signs or symptoms of increased ICP develop and/or there is a progression of ventriculomegaly on imaging, surgical intervention is generally warranted.

CSF Diversion Procedures

Choice of procedure

CSF shunts have long been the standard treatment for hydrocephalus in children. ETV is an alternative approach that has several advantages over CSF shunting in that it is relatively low-cost, durable, and potentially avoids the long-term complications that frequently occur with ventriculoperitoneal (VP) shunts (i.e. infection and/or malfunction).

However, ETV is not effective in all patients. The success of ETV depends on the age of the patient, the cause of hydrocephalus, and previous complications [29-30].

Criteria for selection of patients for ETV versus shunting are not standardized and practice varies considerably. The 2014 evidence-based guidelines of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) concluded that outcomes of the two procedures are generally equivalent and they did not advocate for one approach over the other [31].The ETV success score can help identify patients who are likely to benefit from ETV. In current practice, the following approach is used:

a. It is generally performed ETV for patients with third or fourth ventricular outlet obstruction or with clear aqueductal stenosis and for those with pineal region tumors and tectal tumors because these respond well to ETV.

b. It is generally performed a CSF shunt procedure rather than ETV in patients with a history of IVH, meningitis, or previous shunting because the likelihood of success with ETV is low

in this setting. However, if patients with these disorders also have acquired aqueduct stenosis, generally attempt ETV before pursuing shunting, because it has had moderate success with this approach.

It is generally not performed ETV for treatment of obstructive hydrocephalus in infants <3 months old, because the likelihood of success is low (around 25 percent) in this age group [30].

For children in whom ETV is unsuccessful (ie, hydrocephalus progresses following ETV), generally perform a shunting procedure, because repeating the ETV acutely is not likely to be successful [18].

CSF Shunt

A mechanical shunt system is placed to prevent the excessive accumulation of CSF. The shunt allows CSF to flow from the ventricles into the systemic circulation or to the peritoneum where it is absorbed, bypassing the site of mechanical or functional obstruction to absorption. Shunts consist of the following components:

Ventricular catheter

A catheter is placed into one of the lateral ventricles (usually the right). In placing the ventricular catheter, entry from the skull is directed to access the ventricle without penetrating the eloquent cortex. Frontal or occipital-parietal entry points are most commonly used to position the tip of the catheter in the frontal horn, away from the choroid plexus. The optimal entry point is unclear. A 2014 systematic review of five studies that evaluated the impact of entry points on shunt survival concluded that the available evidence is insufficient to recommend one entry point (frontal or occipital) over the other.

Technical adjuvants such as ventricular endoscopic placement, computer-assisted electromagnetic guidance, or ultrasound guidance are sometimes used to guide the placement of the ventricular catheter; however, the available data are insufficient to determine if the use of these technologies is associated with reduced complication rates and/or improved shunt function [32].

Valve

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 ventricular pressure decreases as fluid drains, resulting in the closure of the valve until the pressure increases again. Many different shunt system components are available and they function with a variety of pressure, flow, and siphon control characteristics [33].

The design of these systems has evolved to reduce failure rates and other complications. Antisiphon devices (either intrinsic in the valve mechanism or as a separate device) have been developed to provide progressive resistance to flow to counteract the siphoning that occurs when negative pressure is exerted with vertical positioning.

Programmable valves allow alterations in valve function to be made without a surgical procedure. A 2014 systematic review of 22 studies comparing different shunt components concluded that the available evidence did not demonstrate a clear advantage for any specific shunt component, mechanism, or valve design over another [33].

Distal catheter

The distal end of the system is connected to a catheter that is most commonly placed in the peritoneal cavity (VP shunt). Less commonly (eg, if the peritoneal placement is not feasible), the distal catheter is inserted in the right atrium of the heart (ventriculoatrial [VA] shunt) or pleural space (ventriculopleural shunt).

Complications

In general, complications of shunted hydrocephalus are due to malfunction of the shunt. If the shunt malfunctions and if the mechanism causing the hydrocephalus is still active, symptoms of hydrocephalus recur, and a shunt revision or other drainage procedure is required.

Malfunction may be caused by infection or mechanical failure. Approximately 40 percent of standard shunts malfunction within the first year after placement, and 5 percent per year malfunction in subsequent years [34].

Infection

Shunt infection is a common complication, occurring in approximately 5 to 15 percent of procedures [34,35].This may lead to ventriculitis, may promote the development of loculated compartments of CSF, and may contribute to impaired cognitive outcome and death. The risk of shunt infections appears to be higher in newborns compared with older infants and children [36]. Most shunt infections occur in the first six months after shunt placement. This is an important consideration in deciding when to tap shunts to evaluate a fever, especially when there is no clinical or radiographic evidence of mechanical shunt failure. Increasing abdominal pain associated with peritoneal signs and/or fever is a common presentation of shunt infection in patients with VP shunts. Abdominal ultrasound may demonstrate pseudocyst. Shunt infection must be considered in a child with a shunt who develops a persistent fever. Antibiotics should be started, but this treatment alone is often not effective. In most cases, an infected shunt must be removed, and an external ventricular drain must temporarily be placed.

Perioperative antibiotic prophylaxis reduces the risk of infection. In two meta-analyses, prophylactic antibiotics in the perioperative period reduced the risk of shunt infection by approximately 50 percent [37]. The use of antibiotic-impregnated catheters also appears to lower the risk of infection [37,38].

Mechanical failure

Mechanical shunt failure is another important cause of shunt failure. Like shunt infection, it is most common during the first year after shunt placement [35]. The majority of shunt failures result from obstruction at the ventricular catheter [35]. Fractured tubing is the cause of shunt failure in approximately 15 percent of cases. Other causes include shunt migration (partial or complete)

and excessive CSF drainage (over drainage). Mechanical failure requires prompt recognition and surgical intervention.

Overdrainage

Overdrainage can cause functional shunt failure, which causes subnormal ICP (particularly in the upright position) and is associated with characteristic neurologic symptoms such as postural headache and nausea [34].

Other complications

Other less common complications are related to the end site of CSF drainage. Potential complications in patients with VP shunts include perforation of the viscus and intestinal obstruction. Patients with VA shunts may develop thrombosis associated with the atrial catheter, cor pulmonale, or very rarely may develop glomerulonephritis ("shunt nephritis"), which is related to chronic infection. Patients with ventriculopleural shunts may develop pleural effusions which occasionally produce symptoms.

Endoscopic third Ventriculostomy

ETV involves creating an opening in the floor of the third ventricle to allow CSF to flow into the prepontine cistern and the subarachnoid space. ETV may be used in the initial treatment of selected cases of obstructive hydrocephalus and as an alternative to shunt revision; it is generally not effective for patients with communicating hydrocephalus (i.e. hydrocephalus resulting from impaired CSF absorption).

Some experts consider ETV the treatment of choice for aqueductal stenosis, although approximately 20 percent of patients still require shunting [39].The success of the procedure depends on the age of the patient, the cause of hydrocephalus, and the previous complications [29-30].

The ETV success score can be used to estimate the likelihood of early success. The score was developed and validated using a dataset of 618 consecutive ETV procedures performed at 12 international institutions [30].Older age at the time of the procedure (i.e. >1 year old) is the strongest predictor of success; other important predictors include noninfectious hydrocephalus etiology (eg, aqueductal stenosis, tectal tumor, myelomeningocele, intraventricular hemorrhage [IVH]), and lack of the previous shunt.

In an analysis of 618 ETV procedures performed at 12 international institutions, the overall success of ETV assessed six months after the procedure was 66 percent [30]. In a follow-up study, the same investigators compared outcomes with ETV and shunting in a cohort of children with newly diagnosed hydrocephalus treated with either ETV (489 patients) or shunt insertion (720 patients) [40]. Among patients with high predicted ETV success (i.e. ETV success score ≥80), cumulative reoperation-free survival at 36 months was greater with ETV compared with shunting (72 percent versus 54 percent). However, among patients with moderate and low ETV success scores, outcomes were similar between the two procedures. For patients with moderate ETV success scores (i.e. 50 to 70), reoperation-free survival at 36 months was approximately 50 percent in both groups; and for those with low ETV success scores (i.e. ≤40), reoperation-free survival at 36 months was approximately 38 percent in both groups. In another multicenter, prospective study involving 336 children who underwent initial ETV and were followed for at least 18 months, 42 percent of patients had documented failure of their ETV requiring repeat hydrocephalus surgery during follow-up [30]. Two-year reoperation-free survival was 58 percent. The majority of failures (83 percent) occurred within six months of surgery and the ETV success score was a strong predictor of success. The cohort represented a selected group of patients; most patients (85 percent) were older than 12 months and most (81 percent) had not undergone prior shunt placement. The most common etiologies were aqueduct stenosis (25 percent) and midbrain or tectal lesions (21 percent). If ETV is performed, it is important to monitor the patient postoperatively with serial clinical examinations and imaging to determine if the procedure was successful. If the hydrocephalus progresses, a shunting procedure generally is performed, because repeating the ETV acutely is not likely to be successful [18].

Complications

Complications of ETV were described in a 2012 systematic review of 24 case series reporting outcomes of >2500 ETV procedures in children and adults with hydrocephalus due to a variety of etiologies, most common tumor (37 percent) and aqueductal stenosis (26 percent) [41].

In a subsequent multicenter prospective study involving 336 ETV procedures in pediatric patients, postoperative complications included CSF leak (4.4 percent), hyponatremia (3.9 percent), pseudomeningocele (3.9 percent), severe bleeding (1.8 percent), thalamic contusion (1.8 percent), venous injury (1.5 percent), hypothalamic contusion (1.5 percent), and major arterial injury (0.3 percent) [30].The visible fornical injury was seen more commonly in this cohort than previously reported (17 percent of cases). New neurologic deficits occurred in 1.5 percent of cases, with 0.5 percent being permanent.

ETV with choroid plexus cauterization

Because of the high rate of failure of ETV, particularly in young infants, researchers have suggested adding choroid plexus cauterization (CPC) to ETV in an attempt to improve the efficacy of the procedure. Based on favorable results in a study performed predominantly in sub-Saharan Africa,[42] the combined ETV and CPC procedure was introduced in the United States and Canada beginning in the late 2000s to early 2010s [43].

In a clinical trial conducted in Uganda, 100 infants with postinfectious hydrocephalus were randomly assigned to undergo ETV with CPC or VP shunt placement [42].Neurodevelopmental outcomes were assessed at 12 months after surgery using the Bayley Scales of Infant Development (BSID) score, which ranges from 1 to 19 and is scaled to a mean of 10±3 for the general population. BSID scores were similarly low in both groups (the median BSID cognitive score in the ETV-CPC group was 4 versus 2 in the VP shunt group). Rates of treatment failure were also similar (35 versus 24 percent, respectively; hazard ratio 0.70, 95% CI 0.3-1.5). Postoperative CSF volume was assessed with neuroimaging and was considerably greater in the ETV-CPC group (410 mL versus 171 mL, respectively). There were no differences

in infection rates (4 percent in both groups). CPC is technically challenging and requires skill with a flexible endoscope. To perform the procedure successfully, the surgeon must access the entire lateral ventricle choroid plexus bilaterally. Inadequate lighting in the ventricle may limit the amount of choroid plexus cauterization and possibly complicate the procedure. In addition, the choroid plexus is not the only site for CSF production, so even if cauterization is successful, the procedure may not adequately address the hydrocephalus in some cases.

FOLLOW-UP

Patients who undergo surgical treatment for hydrocephalus require long-term follow-up with a neurosurgeon. Following the initial surgical intervention, patients should be seen within two to four weeks, or sooner if concerning symptoms develop. Visits can then be spaced out if the child is stable.

Neuroimaging studies are typically obtained postoperatively. Postoperative imaging for children who have undergone endoscopic third ventriculostomy (ETV) should include a magnetic resonance cerebrospinal fluid (CSF) CSF flow study to demonstrate flow through the ventriculostomy.

Once a ventricular size is stabilized on neuroimaging, and the parents are comfortable and familiar with the signs to watch for, follow-up imaging is done once every few years or if the patient presents with symptoms of shunt malfunction.

For children with hydrocephalus, the goals of treatment are to return the CSF flow and intracranial pressure (ICP) to levels that are as near to normal as possible and to promote normal neurologic development. The effectiveness of a surgical intervention is assessed using both clinical and radiologic findings. Neuroimaging indicators that are commonly used for this purpose include [44].

Reduction in ventricle size

(a) Amount of CSF over the cerebral hemispheres

(b) Presence of a flow void in the third ventriculostomy site (for patients who underwent the third ventriculostomy)

(c) Degree of periventricular edema

However, imaging findings do not always correlate with important clinical outcomes such as neurocognitive sequelae. In particular, ventricular size alone appears to be a poor indicator of the success or failure of surgical intervention [44].

Close neurodevelopmental monitoring is an important aspect of the long-term management of children with treated hydrocephalus and should be included in all routine health maintenance visits. If concerns arise, appropriate referrals should be made.

In addition to neuroimaging and neurodevelopmental monitoring, typically follow patients with ventriculoatrial (VA) shunts with yearly cardiac echocardiograms. Unlike ventriculoperitoneal (VP) shunts, VA shunts can manifest with cardiac vegetations and/or cor pulmonale decades after shunt insertion. It is important to understand these long-term complications and to follow patients appropriately into adulthood.

Shunt Malfunction

Prompt evaluation for possible shunt malfunction should be performed in patients with shunts who develop new or worsening signs or symptoms of elevated intracranial pressure (ICP) (eg, headache, vomiting, lethargy, papilledema, irritability). Consultation with a neurosurgeon should occur early on in the evaluation.

Evaluation for shunt malfunction typically includes a detailed neurologic examination, neuroimaging (usually with computed tomography [CT] or rapid brain magnetic resonance imaging [MRI]), and plain radiographs of the shunt tubing pathway (shunt series).

In some cases, a shunt tap by the neurosurgical team may provide useful information (eg, elevated pressure suggestive of shunt malfunction, abnormal cerebrospinal fluid [CSF] indices suggestive of infection).

Shunt malfunction can be diagnosed based on any of the following:

(a) Interval increase in ventricular size on neuroimaging study; however, as many as 30 percent of patients may lack this finding.

(b) Highly concerning neurologic findings (eg, new focal deficits, papilledema, severe lethargy), even in the absence of increased ventricular size.

(c)Fractured, displaced, or kinked shunt tubing seen on imaging (in the setting of suggestive signs or symptoms).

(d) Elevated CSF pressure and/or poor CSF flow as assessed by tapping the shunt.

(e) Persistent symptoms (eg, headaches, vomiting, lethargy) despite appropriate nonsurgical management.

If the findings of the evaluation are not consistent with shunt malfunction, other possible causes of the symptoms should be investigated (eg, infection, seizures, gastrointestinal pathology).

Outcome

The outcome of hydrocephalus depends upon the etiology, the associated abnormalities, and the complications, such as infection.

Survival

Survival in untreated hydrocephalus is poor. Approximately 50 percent of affected patients die before three years of age, and approximately 80 percent die before reaching adulthood.33 Treatment markedly improves the outcome for hydrocephalus not associated with tumor, with 89 and 95 percent survival in two reports [36, 45].

Epilepsy

Seizures occur frequently in children with shunted hydrocephalus [45, 46]. In one report from 802 children treated with ventriculoperitoneal (VP) shunt and followed for a mean of eight years, 32 percent had epilepsy.46 Seizures may be present at the time the diagnosis of hydrocephalus is made. However, shunt

placement and complications are also predisposed to epilepsy.

The incidence of seizures varies according to the etiology of hydrocephalus. In the study described above, the risks in patients with infection, cerebral malformations or intraventricular hemorrhage (IVH), and spina bifida were approximately 50, 30, and 7 percent, respectively [46].

Seizures are associated with poor cognitive outcomes. In the study described above, fewer children with seizures had normal cognition (intelligence quotient [IQ] >90) compared with those without seizures (24 versus 66 percent) [46].

Seizures in this setting can be subclinical or can occur exclusively at night [47]. Electroencephalogram (EEG) monitoring should be considered in patients with neurologic deterioration who do not appear to have shunt failure or infection.

Functional outcome

Functional outcome is dependent on many factors, including a degree of prematurity, other central nervous system (CNS) malformations, other congenital abnormalities, and epilepsy, as well as sensory and motor impairments [33]. The Hydrocephalus Outcome Questionnaire is a useful tool to measure the physical, emotional, cognitive, and social function of hydrocephalic children, aspects of health that are often overlooked [48].

In a study that reported outcomes of 129 children who underwent shunt placement before the age of 2 years between 1979 and 1982 and who were followed up for at least 10 years, motor deficits, visual or auditory deficits, and epilepsy occurred in 60, 25, and 30 percent of patients, respectively [45].

IQ was >90 in 32 percent and was <50 in 21 percent. Attendance at a normal school was possible for 60 percent, although one-half were one to two years behind for their age or were having difficulties. Of the remainder, 31 percent were in special classes or were institutionalized, and 9 percent were not considered educable. In another series of 155 children who underwent first-time VP shunt insertion between 1978 and 1983 and were followed for 10 years, 11 percent died during the follow-up period.36 Among survivors, approximately 60 percent attended a normal school. Children with hydrocephalus caused by infection or by IVH were more likely to need special education services than were those with congenital hydrocephalus (52 and 60 percent versus 29 percent).

In extremely low birth weight infants, hydrocephalus associated with IVH and a shunt correlates with adverse neurodevelopmental outcomes at 18 to 22 months follow-up, compared with children with and without severe IVH and with no shunt [49].

Tuberculous Meningitis

Tuberculous meningitis (TBM) develops in 2 steps. Mycobacterium tuberculosis bacilli enter the host by droplet inhalation. Localized infection escalates within the lungs, with dissemination to the regional lymph nodes. In persons who develop TBM, bacilli seed to the meninges or brain parenchyma, resulting in the formation of small subpial or subependymal foci of metastatic caseous lesions, termed Rich foci. The second step in the development of TBM is an increase in the size of a Rich focus until it ruptures into the subarachnoid space. The location of the expanding tubercle (i.e. Rich focus) determines the type of CNS involvement. Tubercles rupturing into the subarachnoid space cause meningitis. Currently, more than 20 million children 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 is a very critical disease in terms of fatal outcomes and permanent sequelae, requiring rapid diagnosis and treatment. Prediction of prognosis of TBM is difficult because of the protracted course, diversity of underlying pathological mechanisms, variation of host immunity, and virulence of M tuberculosis. Prognosis is related directly to the clinical stage at diagnosis. TBM may have an acute presentation. Sometimes it may present with cranial nerve deficits, or it may have a more indolent course involving headache, meningismus, and altered mental status. The prodrome is usually nonspecific, including headache, vomiting, photophobia, and fever. The duration of presenting symptoms may vary from 1 day to 9 months. TBM continues to pose a diagnostic problem. A high index of clinical suspicion is essential. 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 particular 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 abscesses. The diagnosis of TBM cannot be made or excluded solely based on clinical findings. Tuberculin testing is of limited value. Variable natural history and accompanying clinical features of TBM hinder the diagnosis. A spinal tap carries some risk of herniation of the medulla in any instance when intracranial pressure (ICP) is increased (eg, TBM), but if meningitis is suspected, the procedure must be performed regardless of the risk. CNS imaging modalities lack specificity but help in monitoring complications that require neurosurgery. Prompt treatment is essential; death may occur as a result of missed diagnoses and delayed treatment. Antimicrobial therapy is best started with isoniazid, rifampin, and pyrazinamide; the addition of a fourth drug is left to local choice. The optimal duration of antimicrobial therapy is unclear. The benefits of adjuvant corticosteroids remain in doubt: their use in adults is controversial, though they may be indicated in the presence of increased ICP, altered consciousness, focal neurological findings, spinal block, and tuberculous encephalopathy. 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. Prompt shunting improves outcomes, particularly in patients presenting with minimal neurological deficits. New research avenues include research into

vaccine design, mechanisms of drug resistance, and virulence determinants. Rapid sensitivity testing using bacteriophages considers the problem of drug resistance.

Pathophysiology

Many of the symptoms, signs, and sequelae of tuberculous meningitis (TBM) are the result of an immunologically directed inflammatory reaction to the infection. TBM develops in 2 steps. Mycobacterium tuberculosis bacilli enter the host by droplet inhalation, the initial point of infection being the alveolar macrophages.

Localized infection escalates within the lungs, with dissemination to the regional lymph nodes to produce the primary complex. During this stage, short but significant bacteremia is present that can seed tubercle bacilli into other organs. In persons who develop TBM, bacilli seed to the meninges or brain parenchyma, resulting in the formation of small subpial or subependymal foci of metastatic caseous lesions. These are termed Rich foci, after the original pathologic studies of Rich and McCordick [50]. Tuberculous pneumonia develops with heavier and more prolonged tuberculous bacteremia. Dissemination to the central nervous system (CNS) is more likely, particularly if miliary tuberculosis (TB) develops. The second step in the development of TBM is an increase in the size of a Rich focus until it ruptures into the subarachnoid space. The location of the expanding tubercle (i.e. Rich focus) determines the type of CNS involvement.

Tubercles rupturing into the subarachnoid space cause meningitis. Those deeper in the brain or spinal cord parenchyma cause tuberculomas or abscesses. While an abscess or hematoma can rupture into the ventricle, a Rich focus does not. A thick gelatinous exudate infiltrates the cortical or meningeal blood vessels, producing inflammation, obstruction, or infarction. Basal meningitis accounts for the frequent dysfunction of cranial nerves (CNs) III, VI, and VII, eventually leading to obstructive hydrocephalus from obstruction of basilar cisterns. Subsequent neurological pathology is produced by 3 general processes: adhesion formation, obliterative vasculitis, and encephalitis or myelitis.

Formation of tuberculomas

Tuberculomas are conglomerate caseous foci within the substance of the brain. Centrally located, active lesions may reach considerable size without producing meningitis [50]. Under conditions of poor host resistance, this process may result in focal areas of cerebritis or frank abscess formation, but the usual course is the coalescence of caseous foci and fibrous encapsulation (i.e. tuberculoma).

Tuberculomas may coalesce together or grow in size, even during ongoing antitubercular therapy [51]. This process may have an immunological basis [52]. Tuberculomas can also involve the adjacent intracranial trunk artery, largely causing vasculitis [53]. The probable embolic spread of tuberculomas in the brain in multidrug-resistant TBM has been reported [54].

Spinal involvement

In the tuberculous process, the spinal meninges may be involved, owing to the spread of infection from intracranial meningitis, primary spinal meningitis in isolation as a result of a tuberculous focus on the surface of the cord rupturing into the subarachnoid space, or transdural extension of infection from caries of the spine.

Pathologically, a gross granulomatous exudate fills the subarachnoid space and extends over several segments. Vasculitis involving arteries and veins occurs, sometimes resulting in ischemic spinal cord infarction. The earliest lesion in the vertebra is invariably due to hematogenous spread, often involving the body of the vertebra near an intervertebral disk. The intervertebral disk is almost always involved with the spread of the disease to the adjacent vertebra and eventually along the anterior or posterior longitudinal ligaments or through the end plate. Soon, a cold abscess develops, either as a paraspinal abscess in the dorsal and lumbar regions or as a retropharyngeal abscess in the cervical region.

As the disease progresses, increasing decalcification and erosion result in a progressive collapse of the bone and destruction of intervertebral disks, involving as many as 3-10 vertebrae in one lesion, resulting in kyphosis. The abscess may rupture intraspinal, resulting in primary spinal meningitis, hyperplastic peripachymeningitis, intraspinal abscess, or tuberculoma.

Pathological Effects on Other Organs

Papilledema is the most common visual effect of TBM. In children, papilledema may progress to primary optic atrophy and blindness resulting from the direct involvement of the optic nerves and chiasma by basal exudates (ie, opticochiasmatic arachnoiditis). In adults, papilledema may progress more commonly to secondary optic atrophy, provided the patient survives long enough. Other causes of visual impairment include chorioretinitis, optic neuritis, internuclear ophthalmoplegia, and, occasionally, 1 abrupt onset of painful ophthalmoplegia.

Ocular involvement is rare in TB. When it occurs, the typical lesion is often a choroidal granuloma. Baha Ali and coworkers describe 3 cases of choroidal TB associated with 3 different clinical situations, including tuberculous meningitis, multifocal TB, and military TB with HIV [55].

CN VI is affected most frequently by TBM, followed by CNs III, IV, VII, and, less commonly, CNs II, VIII, X, XI, and XII [56].

Sudden onset of focal neurological deficits, including monoplegia, hemiplegia, aphasia, and tetraparesis, has been reported. Although these could be postictal phenomena, they mostly are due to vasculitic changes resulting in ischemia. While some of these could be the result of proliferative arachnoiditis or hydrocephalus, vasculitis still appears to be the leading cause. Vasculitis with resultant thrombosis and hemorrhagic infarction may develop in vessels that traverse the basilar or spinal exudate or lie within the brain substance. Mycobacterium also may invade the adventitia directly and initiate the process of vasculitis.

An early neutrophilic reaction is followed by infiltration of lymphocytes, plasma cells, and macrophages, leading to progressive destruction of the adventitia, disruption of elastic fibers, and, finally, intimal destruction. Eventually, fibrinoid

degeneration within small arteries and veins produces aneurysms, multiple thrombi, and focal hemorrhages, alone or in combination [57].

Tremor is the most common movement disorder seen in the course of TBM. In a smaller percentage of patients, abnormal movements, including choreoathetosis and hemiballismus, have been observed, more so in children than in adults. In addition, myoclonus and cerebellar dysfunction have been observed. Deep vascular lesions are more common among patients with movement disorders.

Etiology

The causative organism is Mycobacterium tuberculosis. Various risk factors have been identified.

The first description of TBM is credited to Robert Whytt, based on his 1768 monograph, Observations of Dropsy in the Brain. TBM first was described as a distinct pathological entity in 1836, and Robert Koch demonstrated that TB was caused by M tuberculosis in 1882.

M tuberculosis is an aerobic gram-positive rod that stains poorly with hematoxylin and eosin (H&E) because of its thick cell wall that contains lipids, peptidoglycans, and arabinomannans. The high lipid content in its wall makes the cells impervious to Gram staining. However, the Ziehl-Neelsen stain forms a complex in the cell wall that prevents decolorization by acid or alcohol, and the bacilli are stained a bright red, which stands out clearly against a blue background. Mycobacteria vary in appearance from spherical to short filaments, which may be branched. Although they appear as short to moderately long rods, they can be curved and frequently are seen in clumps. Individual bacilli generally are 0.5-1 µm in diameter and 1.5-10 µm long. They are nonmotile and do not form spores. One of the distinct characteristics of mycobacteria is their ability to retain dyes within the bacilli that usually are removed from other microorganisms by alcohols and dilute solutions of strong mineral acids such as hydrochloric acid. This ability is attributed to a waxlike layer composed of long-chain fatty acids, the mycolic acids, in their cell wall. As a result, mycobacteria are termed acid-fast bacilli.

Risk Factors

Human migration plays a large role in the epidemiology of TB. Massive human displacement during wars and famines has resulted in increased case rates of TB and an altered geographic distribution. With the advent of air travel, TB has a global presence. In the United States, the prevalence of TB, mostly in foreign-born persons, has steadily increased. Once infected with M tuberculosis, HIV co-infection is the strongest risk factor for progression to active TB; the risk has been estimated to be as great as 10% per year, compared with a 5-10% lifetime risk among persons with TB but not HIV infection. Although patients who have HIV infection and TB are at increased risk for TBM, the clinical features and outcomes of TB do not seem to be altered by HIV. Patients infected with HIV, especially those with AIDS, are at very high risk of developing active TB when exposed to a person with infectious drug-susceptible or drug-resistant TB. They have a higher incidence of drug-resistant TB, in part due to Mycobacterium avium-intracellulare, and have worse outcomes. Other predisposing factors for the development of active TB include malnutrition, alcoholism, substance abuse, diabetes mellitus, corticosteroid use, malignancy, and head trauma. Homeless persons, people in correctional facilities, and residents of long-term care facilities also have a higher risk of developing active TB compared with the general population.

Epidemiology

TB is the seventh leading cause of death and disability worldwide. In 1997, TBM was the fifth most common form of extrapulmonary TB. TBM accounted for 5.2% (186) of all cases of exclusively extrapulmonary disease and 0.7% of all reported cases of TB.

United States statistics

Between 1969 and 1973, TBM accounted for approximately 4.5% of the total extrapulmonary TB morbidity in the United States. Between 1975 and 1990, 3,083 cases of TBM were reported by the US Centers for Disease Control and Prevention (CDC), an average of 193 cases per year, accounting for 4.7% of total extrapulmonary TB cases during those 16 years.

In 1990, however, 284 cases of TBM were reported, constituting 6.2% of the morbidity attributed to extrapulmonary TB. This increase in TBM was most likely due to increasing CNS TB among patients with HIV/AIDS and the increasing incidence of TB among infants, children, and young adults of minority populations.

Data suggest that TBM accounts for 2.1% of pediatric cases and 9.1% of extrapulmonary TB cases [58]. TB accounts for approximately 0.04% of all cases of chronic suppurative otitis media [59].

The Tuberculosis: Advocacy Report released by the World Health Organization (WHO) in 2003 suggests the persistence of TB otitis, as well as possibly an increase in the incidence of TB otitis [60]. Tuberculomas account for 10-30% of intracranial masses in TB-endemic areas.

International statistics

The WHO estimates that one-third of the world's population is infected by M tuberculosis. The WHO's 2003 publication Tuberculosis: Advocacy Report stated that 8 million new cases of TB are reported annually and 2 million deaths occur each year [60].

An estimated 8.8 million new TB cases were recorded in 2005 worldwide, 7.4 million in Asia and sub-Saharan Africa. A total of 1.6 million people died from TB, including 195,000 patients infected with HIV [61].

In 2005, the TB incidence rate was stable or in decline in all 6 WHO regions. However, the total number of new TB cases was still rising slowly; the caseload continues to grow in the African, eastern Mediterranean, and Southeast Asia regions [62].

In many areas of Africa and Asia, the annual incidence of TB infection for all ages is approximately 2%, which would yield an estimated 200 cases of TB per 10,000 population per year. Approximately 15-20% of these cases occur in children younger than 15 years.

The worldwide prevalence of TB in children is difficult to assess because data are scarce and poorly organized. The available reports grossly underestimate the true incidence. The lack of surveillance testing in most areas of the world restricts the ability to assess the prevalence of the disease.

The developing world has 1.3 million cases of TB and 40,000 TB-related deaths annually among children younger than 15 years. In the developing world, 10-20% of persons who die of TB are children. TBM complicates approximately 1 of every 300 untreated primary TB infections.

Age Distribution for Tbm

Before the appearance of HIV, the most important determinant for the development of TBM was age. Data published in 2000 revealed that the risk increased with age across racial and ethnic groups.

In populations with a low prevalence of TB, most cases of TBM occur in adults. In the United States in 1996, case rates were low in infancy and decreased somewhat during early childhood. After the age of puberty, they showed a steady increase with age. In general, however, TBM is more common in children than in adults, especially in the first 5 years of life. Children aged 0-5 years are affected more commonly with TBM than any other age group. TBM is uncommon, however, in children younger than 6 months and almost unheard of in infants younger than 3 months because the causative pathological sequence takes at least 3 months to develop. Children, aged 5-14 years often have been referred to as the favored age because they have lower rates of TB than any other age group. Younger children are more likely to develop meningeal, disseminated, or lymphatic TB, whereas adolescents more frequently present with pleural, genitourinary, or peritoneal disease. Childhood TB has a limited influence on the immediate epidemiology of the disease because children rarely are a source of infection to others.

Sex Distribution for Tbm

Among persons younger than 20 years, TB infection rates are similar for both sexes; the lowest rates are observed in children aged 5-14 years. During adulthood, TB infection rates are consistently higher for men than for women; the male-to-female ratio is approximately 2:1.

Prognosis

TBM is a very critical disease in terms of fatal outcomes and permanent sequelae, requiring rapid diagnosis and treatment. The number of deaths due to TB has decreased dramatically since 1953. In 1953, 19,707 deaths from TB were reported in the United States, for a rate of 12.4 deaths per 100,000 population. In 1997, 1,166 deaths were reported, for a rate of 0.4 deaths per 100,000 population.

The number of TB deaths and the TB death rate increased slightly during a recent TB resurgence, reaching a high in 1989 of 1,970 deaths and a rate of 0.8 deaths per 100,000 population before decreasing again.

Patients with TBM continue to do poorly in the long term, despite optimal anti-tuberculous therapy. While increasing age and co-infection with HIV might offer some explanation, they do not explain the whole picture [63].

Prediction of outcome

Prediction of prognosis of TBM is difficult because of the protracted course, diversity of underlying pathological mechanisms, variation of host immunity, and virulence of M tuberculosis. Prognosis is related directly to the clinical stage at diagnosis. Initially, only clinical indices were used for predicting the outcome, such as level of consciousness, stage of meningitis, bacillus Calmette-Guérin (BCG) vaccination status, cerebrospinal fluid (CSF) findings, and evidence of raised intracranial pressure (ICP).

After computed tomography (CT) scanning became available, radiological findings, such as hydrocephalus, infarction, the severity of exudate, and tuberculoma, also were considered for predicting the prognosis of TBM. A recent study that looked at clinical parameters, laboratory studies, and CT scan features in 49 adults and children with TBM used a multivariate logistic regression model to show that the most significant variables for predicting outcome in TBM were age, stage of disease, focal weakness, CN palsy, and hydrocephalus [64]. Children with advandiseasesease with neurological complications have poor outcomes. The occurrence of a syndrome of inappropriate diuretic hormone secretion (SIADH) is common and is also linked to a poor prognosis. Few studies on neurophysiological changes are reported in TBM. EEG has been reported to be useful in assessing the gravity of lesions and was reported recently to help in the prediction of outcomes. Motor evoked potentials and somatosensory evoked potentials also have been reported recently to predict a 3-month outcome of TBM. Misra et al found that focal weakness, Glasgow Coma Scale score, and somatosensory evoked potential findings were the best predictors of 6-month outcome in patients with TBM [65]. Hydrocephalus was the only factor shown to be significant in predisposing patients with TBM who had positive culture results to a poorer outcome. A trend toward a poorer prognosis was also seen in those with advanced stages of the disease. While clinical features in children with TBM who were also infected with HIV and those who were not co-infected with HIV were not markedly different, abnormal radiological findings were more common in the HIV-infected group and outcomes were considerably worse. Coexisting HIV encephalopathy and diminished immune competence undoubtedly contributed to the more severe clinical and neuroradiological features.

History

Tuberculous meningitis (TBM) is difficult to diagnose, and a high index of suspicion is needed to make an early diagnosis. Inquire about the patient's medical and social history, including recent contact with patients with tuberculosis (TB). Elicit any known history of a positive result on the purified protein derivative test, especially a recent conversion. Determine if the patient has a history of immunosuppression from a known disease or drug therapy. Check if the patient has a negative history of bacillus Calmette-Guérin (BCG) vaccination. Walker et al reported that BCG vaccination is partially protective against TB meningitis;

therefore, a history of BCG vaccination or the presence of a BCG vaccination scar affords some degree of reassurance when considering a diagnosis of TBM (grade C) [66]. In patients in whom TBM is suspected clinically, the diagnosis must be rigorously investigated; a history of BCG vaccination does not rule out the diagnosis (grade C). In an immunocompetent individual, central nervous system (CNS) TB usually takes the form of meningitis which causes an acute-to-subacute illness characterized by fever, headache, drowsiness, meningism, and confusion over approximately 2-3 weeks. Usually, during the prodromal period, nonspecific symptoms are present, including fatigue, malaise, myalgia, and fever. In one study, only 2% of patients reported meningitic symptoms. The duration of presenting symptoms may vary from 1 day to 9 months, although 55% presented with symptoms of less than 2 weeks duration.

Often, in the first stage of meningitis, patients have an infection of the upper respiratory tract, a fact that should be remembered when the concurrent fever and irritability or lethargy seem out of proportion to the obvious infection or when general symptoms persist after improvement in the local manifestations. Fever and headache can be absent in 25% of patients, and malaise can be absent in as many as 60% of patients. Headache and mental status changes are much more common in elderly persons. Sudden onset of focal neurologic deficits, including monoplegia, hemiplegia, aphasia, and tetraparesis, has been reported. Tremor and, less commonly, abnormal movements, including choreoathetosis and hemiballismus, have been observed, more so in children than in adults. Myoclonus and cerebellar dysfunction have also occurred. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion is a common complication and is linked to a poor prognosis. Less frequent presentations include atypical febrile seizures in children, isolated cranial nerve (CN) palsies, bilateral papilledema, and an acute confusional state.

Tuberculous Spinal Meningitis

Tuberculous spinal meningitis may manifest as an acute, subacute, or chronic form. The clinical picture in primary spinal meningitis is often characterized by myelopathy, with progressive ascending paralysis, eventually resulting in basal meningitis and associated sequelae. In some cases with acute onset, in addition to variable constitutional symptoms, patients develop acute paraplegia with sensory deficits and urinary retention. The clinical picture often mimics transverse myelitis or Guillain-Barré syndrome. The subacute form is often dominated by myeloradiculopathy, with radicular pain and progressive paraplegia or tetraplegia. A less virulent chronic form might mimic a very slowly progressive spinal cord compression or nonspecific arachnoiditis. The dorsal cord seems to be affected most commonly, followed by the lumbar and cervical regions.

Tuberculous spondylitis

Tuberculous spondylitis is also known as Pott disease or spinal caries. In regions where the disease is endemic, such as Asia and Africa, this condition still accounts for 30-50% of all cases of compressive myelopathy resulting in paraplegia. Spinal TB also accounts for approximately 50% of all bone and joint TB cases.

In the lumbar region, tuberculous spondylitis may result in a psoas abscess that often calcifies. It usually runs a subacute or a chronic course, with back pain and fever, and variable neurological deficits. Spondylitis can also result in various symptoms, including local and radicular pain, limb motor and sensory loss, and sphincter disturbances.

Serous Tuberculous Meningitis and Tuberculous Encephalopathy

Two rare forms of TBM are serious TB meningitis and TB encephalopathy. Serious TB meningitis is characterized by signs and symptoms of mild meningitis with spontaneous recovery.

TB encephalopathy usually occurs in a young child with progressive primary TB; the presentation is that of reduced levels of consciousness with few focal signs and minimal meningism. Diffuse edema and white matter pallor with demyelination are found upon pathologic examination. The pathogenesis is uncertain but is presumed to be immune-mediated. Diagnosis is important because anecdotal reports suggest a good response to corticosteroids.

Tuberculous Radiculomyelitis

Tuberculous radiculomyelitis (TBRM) is a rare complication of TBM.

Physical Examination

Perform careful general, systemic, and neurologic examinations, looking especially for lymphadenopathy, papilledema, and tuberculomas during funduscopy, and meningismus. Look also for a BCG vaccination scar. Because BCG vaccination is partially protective against TB meningitis, the presence of a BCG vaccination scar affords some degree of reassurance when considering a diagnosis of TBM [66]. Nevertheless, prior BCG vaccination does not rule out the diagnosis.

Visual findings

Apart from papilledema, fundus examination occasionally reveals a retinal tuberculoma or a small grayish-white choroidal nodule, highly suggestive of TB. These lesions are believed to be more common in miliary TB than in other forms of TB. In children, fundus examination may reveal pallor of the disc. The examination may elicit visual impairment.

Neurologic Findings

Cranial neuropathies, most often involving CN VI, may be noted. CNs III, IV, VII, and, less commonly, CNs II, VIII, X, XI, and XII, also may be affected. Focal neurological deficits may include monoplegia, hemiplegia, aphasia, and tetraparesis.

Tremor is the most common movement disorder seen in the course of TBM. In a smaller percentage of patients, abnormal movements, including choreoathetosis and hemiballismus, have been observed, more so in children than in adults. In addition, myoclonus and cerebellar dysfunction have been observed. Deep vascular lesions are more common among patients with movement disorders.

Complications

TBRM is a complication of TBM that has been reported only rarely in the modern medical literature. It develops at various intervals after TBM, even in adequately treated patients after sterilization of the CSF. The most common symptoms are subacute paraparesis, radicular pain, bladder disturbance, and subsequent paralysis.

Staging

In 1948, the British Medical Research Council developed a method for staging the severity of the disease, as follows:

Stage I describes the early nonspecific symptoms and signs including apathy, irritability, headache, malaise, fever, anorexia, nausea, and vomiting, without any alteration in the level of consciousness

Stage II describes altered consciousness without coma or delirium but with minor focal neurological signs; symptoms and signs of meningism and meningitis are present, in addition to focal neurological deficits, isolated CN palsies, and abnormal involuntary movements

Stage III describes an advanced state with stupor or coma, dense neurological deficits, seizures, posturing, and/or abnormal movements

Approach Considerations

The diagnosis of tuberculous meningitis (TBM) cannot be made or excluded based on clinical findings. Tuberculin testing is of limited value. Variable natural history and accompanying clinical features of TBM hinder the diagnosis [67-68].

Spinal tap carries some risk of herniation of the medulla in any instance when intracranial pressure (ICP) is increased (eg, TBM), but if meningitis is suspected, the procedure must be performed regardless of the risk, using suitable precautions and obtaining informed consent before the procedure.

Ziehl-Neelsen staining lacks sensitivity, and culture results are often too late to aid clinical judgment. Semiautomated radiometric culture systems, such as the Bactec 460, and automated continuously monitored systems have reduced culture times. Newer methods involving the amplification of bacterial DNA by polymerase chain reaction (PCR) and comparable systems have not been assessed completely and may not be suitable for laboratories in developing countries with limited resources.

A complete blood count should be performed, and the erythrocyte sedimentation rate should be determined.

The serum glucose level should be measured; this value is a useful comparison with the glucose level measured in the cerebrospinal fluid (CSF).

Serologic testing for syphilis should be performed. Complementation testing or its equivalent for fungal infections should also be performed.

Serum And Urine Chemistry Studies

Electrolyte concentrations should be assessed. Mild-to-moderate hyponatremia is present in roughly 45% of patients, in some cases constituting a true syndrome of inappropriate diuretic hormone secretion (SIADH). Blood urea nitrogen (BUN) and creatinine levels should be measured as well.

Lumbar Puncture

Use manometry to check CSF pressure. Typically, the pressure is higher than normal.

Inspect the CSF visually and note its gross appearance. It typically is clear or slightly turbid. If the CSF is left to stand, a fine clot resembling a pellicle or cobweb may form. This faintly visible "spider's web clot" is due to the very high level of protein in the CSF (ie, 1-8 g/L, or 1000-8000 mg/dL) typical of this condition. Hemorrhagic CSF also has been recorded in proven cases of TBM; this is attributed to fibrinoid degeneration of vessels resulting in hemorrhage (Smith, 1947).

CSF analysis

Tests that may be performed on CSF specimens obtained by lumbar puncture include the following:

Cell counts, differential count, cytology

Glucose level, with a simultaneous blood glucose level

Protein level

Acid-fast stain, Gram stain, appropriate bacteriologic culture and sensitivity, India ink stain

Cryptococcal antigen and herpes antigen testing

Culture for Mycobacterium tuberculosis (50-80% of known cases of TBM yield positive results)

PCR

Results imply that PCR can provide a rapid and reliable diagnosis of TBM, although false-negative results potentially occur in samples containing very few organisms (< 2 colony-forming units per mL).

Syphilis serology

CSF typically has pleocytosis, an elevated protein level, and marked hypoglycorrhachia.

In children, these numbers are 200 cells/µL (range, 5-950 cells/µL), 21% (range, 15-30%), and 3% (range, 1-5%), respectively.

The mean protein level in adults averages 224 mg/dL (range, 20-1000 mg/dL), and in children it is 219 mg/dL (range, 50-1300 mg/dL). The proportion with a normal protein content averages 6% (range, 0-15%) for adults and 16% (range, 10-30%) for children.

The proportion with depressed glucose levels (< 45 mg/dL or 40% of serum glucose) averages 72% (range, 50-85%) for adults and 77% (range, 65-85%) for children.

A positive smear result is present in an average of 25% (range, 5-85%) of adults and only 3% (range, 0-6%) of children, whereas the numbers with a positive CSF culture average 61% (range, 40-85%) and 58% (range, 35-85%) for adults and children, respectively. Failure to respond to treatment should prompt a

search for fungal infections or malignancies.

Chest Radiography

Chest radiography posteroanterior and lateral views may reveal hilar lymphadenopathy, simple pneumonia, infiltrate, fibronodular infiltrate/cavitation, and/or pleural effusion/pleural scar.

Brain and Spinal Imaging

CT scanning and MRI of the brain reveal hydrocephalus, basilar meningeal thickening, infarcts, edema, and tuberculomas. Although they lack specificity, they help in monitoring complications that require neurosurgery.

Imaging studies, both CT scanning and MRI, are performed with and without enhancement, as long as the renal function of the patient is not compromised.

Basal cisterns often enhance strikingly, corresponding to the thick exudate that is observed pathologically. The quadrigeminal cistern, interpeduncular fossa, ambient cistern, and chiasmatic region are particularly involved, owing to associated arachnoiditis. Meningeal enhancement is more common in HIV-infected patients.

Contrast enhancement further delineates focal parenchymal and space-occupying lesions, with or without associated hydrocephalus.

Srikanth et al concluded that CT features of TBM in elderly patients were few, atypical, and noncontributory for diagnosis, probably because of age-related immune senescence [69]. Hence, strong clinical suspicion and correlation with laboratory findings are necessary for early diagnosis.

For tuberculous spinal meningitis, MRI shows that the subarachnoid space is obliterated, with a focal or diffusely increased intramedullary signal on T2-weighted images and variable degrees of edema and mass effect.

Most spinal cord lesions appear hyperintense on T2-weighted images and isointense or hypointense on T1-weighted images. MRI findings in patients with spinal cord TB have both diagnostic and prognostic significance. Cord atrophy or cavitation and the presence of syrinx on MRIs may be associated with a poor outcome [50].

Materials & Methods

Operational Definitions

Tuberculous Meningitis:

Patients had either of the following signs.

Fever (Temperature above 100 oF) for more than 15 days

Altered Conscious Level (GCS 14 or less).

Headache.

Weight loss (>5 kg during last 1 month).

Fits (one or more episodes of involuntary movements of one or more parts of the body last 1 week)

CSF analysis i.e. WBC Count > 10/mm

Hydrocephalus

Enlargement of ventricles (size of both temporal horns of lateral ventricles more than 2 mm) on MRI.

Obstructive Hydrocephalus:

Enlargement of the lateral and third ventricles (>2 mm) but no enlargement of the fourth ventricle on MRI brain.

Materials and Methods

Study Design:

Cross-Sectional Study

Study Setting:

The study was carried out at the Medical, Neurology, and Neurosurgery Departments of Children Hospital, Lahore.

Duration of Study:

November 30, 2020, to May 30, 2021

Sample Size:

The sample size was calculated as 278 by 95% confidence level with a 3% margin of error and taking an expected frequency of obstructive hydrocephalus as 7% in patients with TB meningitis.7

Sampling Technique:

Non-Probability Consecutive Sampling

Sample Selection

Inclusion Criteria

All patients of tuberculous meningitis aged 6 months to 12 years of either gender meeting the above operational definition were included in this study

Exclusion Criteria

Children with congenital central nervous system malformations.

Developmentally delayed children (on history/medical record)

Data Collection Procedure

After approval of the ethical committee, 278 Patients with Tuberculous meningitis fulfilling the operational definition were selected for the study. Patients were labeled as having obstructive hydrocephalus as per a report of their MRI brain done by a single consultant radiologist to avoid bias. Tuberculous meningitis and obstructive hydrocephalus were managed as per hospital protocol. All the data were collected on a pre-designed proforma (attached).

Data analysis plan

Statistical package for the social sciences (SPSS) v25.0 software was used to analyze the collected data. Mean and standard deviation was calculated for quantitative variables like age.

Qualitative variables like obstructive hydrocephalus and gender were presented as frequency and percentage. Data were stratified for age, gender, and duration of TBM. Post-stratification, a Chi-square test was applied. A p-value ≤0.05 was considered significant.

Results

In this study, 278 patients who had tuberculous meningitis fulfilling the selection criteria were included from the Medical, Neurology, and Neurosurgery Departments of Children Hospital, Lahore.

Among these patients, 159(57.2%) were males and 119(42.8%) were females. 20(7.2%) were between 6 months-1 year age group, while 53(19.1%) and 205(73.7%) were between 1-3 and 3-12 years age groups respectively. The mean age of the patients was 6.2±2.3 years with 6 months and 12 years as minimum and maximum ages.

Among these patients, 99(35.6%) had a duration of TBM <1 month, while 93(33.5%) and 86(30.9%) had between 1-3 and >3 months respectively.

Among these patients, 61(21.9%) patients had obstructive hydrocephalus.

By applying the Chi-Square test, it was concluded that there was no significant difference among gender, age group, and duration of TBM with obstructive hydrocephalus (p>0.362, 0.971, 0.665) respectively **[Tables 1 -7]**.

Discussion

Tuberculosis meningitis (TBM) is a serious public health problem in developing countries as it leads to significant mortality and residual neurological squeal. The estimated mortality due to TBM in Asia is 1.5 per 100,000 population. Obstructive Hydrocephalus was seen in 21.9% of cases of TBM in this study. Similar percentages were seen in a study by Nabi S et al and Thwaites GE et al who had it in around 25% of the cases [70, 71, 72]. However, lower percentages were seen in a study conducted by Chan et al who found it in 15% of the cases [73].Why is this Obstructive hydrocephalus found comparatively higher in our study than the ones with lower percentages, it might be the cut-off value used in this study, which was quite on the lower side, that's why it is reflected in a very higher number. And the other studies

Table 1: Frequency distribution of gender.

Gender	Frequency	Percent
Male	159	57.2
Female	119	42.8
Total	278	100

Table 2: Frequency distribution of age.

Age Groups	Frequency	Percent
6 months - 1 year	20	7.2
1-3 years	53	19.1
3-12 years	205	73.7
Total	278	100

Table 3: Frequency distribution of duration of TBM.

Duration of Tuberculous Meningitis (TBM) (months)	Frequency	Percent
<1 month	99	35.6
1-3 months	93	33.5
>3 months	86	30.9
Total	278	100

Table 4: Frequency distribution of obstructive hydrocephalus.

Obstructive Hydrocephalus	Frequency	Percent
Yes	61	21.9
No	217	78.1
Total	278	100

Table 5: Stratification of obstructive hydrocephalus with respect to gender.

Gender	Obstructive Hydrocephalus			Total	p-value
	Yes	No			
Male	38	121	159	0.362	
	23.90%	76.10%	100.00%		
Female	23	96	119		
	19.30%	80.70%	100.00%		
Total	61	217	278		
	21.90%	78.10%	100.00%		

Table 6: Stratification of obstructive hydrocephalus with respect to age.

Age Groups	Obstructive Hydrocephalus		Total	p-value
	Yes	No		
6 months - 1 year	4	16	20	0.971
	20.00%	80.00%	100.00%	
1-3 years	12	41	53	
	22.60%	77.40%	100.00%	
3-12 years	45	160	205	
	22.00%	78.00%	100.00%	
Total	61	217	278	
	21.90%	78.10%	100.00%	

Table 7: Stratification of obstructive hydrocephalus with respect to duration of TBM.

Duration of Tuberculous Meningitis (TBM) (months)	Obstructive Hydrocephalus		Total	p-value
	Yes	No		
<1 month	23	76	99	0.665
	23.20%	76.80%	100.00%	
1-3 months	22	71	93	
	23.70%	76.30%	100.00%	
>3 months	16	70	86	
	18.60%	81.40%	100.00%	
Total	61	217	278	
	21.90%	78.10%	100.00%	

with similar percentages also had a lower threshold to label it. Obstructive Hydrocephalus was seen marginally higher in a male group where it was caused in 23.9% versus 19.3%. A higher percentage of males were seen in other studies by Kumar R and Christensen et al but they did not find any significant association [74, 75]. Why this was higher in our study, might be because the males presented maximum in stage-II of TBM, which was the group who showed maximum Obstructive hydrocephalus in this study. In the context of age groups with respect to Obstructive hydrocephalus, it was seen maximum in patients with an age group of 1 to 3 years affecting 22.6% of its respective group. It was followed by 3 to 12 years affecting 22.0% of cases, though this difference was not found statistically significant with a p-value of 0.971. Similar higher percentages were seen in other studies by Hoşoğlu S, Anderson NE, and Molavi et al. [76]. Hydrocephalus is one of the most common complications of tuberculous meningitis.3 A study in Pakistan showed that 58% of tuberculous meningitis patients developed hydrocephalus [4]. It is almost always present in patients who have had the disease for four to six weeks [5]. It could be either the communicating or the obstructive type with the former being more frequently seen. In a study done in South Africa, hydrocephalus was communicating in 79% and non-communicating in 7%.[7]. A study done in Malaysia showed hydrocephalus in tuberculous meningitis to be 62% of which 73% had obstructive hydrocephalus and 27% had communicating hydrocephalus [8].

Conclusions

Obstructive Hydrocephalus is an important and deadly complication of tuberculous meningitis and even its low presence cannot be ignored. Management and assessment of Obstructive Hydrocephalus in children with Tuberculous meningitis should be carefully monitored.

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