Pathophysiology and Classification of hydrocephalus

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Abstract

Hydrocephalus is one of the oldest neurologic pathologies recorded in human history, with multiple descriptions by Galen and Hippocrates. Despite the passage of more than two millennia from these early accounts, hydrocephalus remains a common, enigmatic, and challenging entity to treat. Most modern surgical management strategies for obstructive and non-obstructive hydrocephalus have followed evolving cerebrospinal fluid (CSF) shunting strategies. However, recent advances in our understanding of hydrodynamic dysfunctions underlying hydrocephalus have spurred intervention strategies that focus on restoring normal physiologic CSF circulation rather than on external drainage. Neuroendoscopy, a vital tool in the minimally invasive paradigm, affords maximum access to the ventricular system. An imbalance in this CSF production and absorption, leading to net accumulation of fluid and an enlargement of the brain ventricles, leads to hydrocephalus. The balance between production and absorption of CSF is critically important. The resulting pressure of the fluid against the brain tissue causing signs and symptoms of raised pressure is what constitutes hydrocephalus.

Keywords: Hydrocephalus, Pathophysiology

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Introduction

Hydrocephalus (from Greek hydro-, meaning "water", and kephalos, meaning "head")Although a precise definition is controversial, hydrocephalus defined as an active distension of the ventricular system resulting from inadequate passage of cerebrospinal fluid from its point of production within the cerebral ventricles to its point of absorption into the systemic circulation **(Rizvi RA et al .,2005)**

or generally refers to a disorder of cerebrospinal fluid (CSF) physiology resulting in abnormal expansion of the cerebral ventricles, typically associated with increased intracranial pressure. **(Harris CA et al .,2021)**

Hydrocephalus is one of the oldest neurologic pathologies recorded in human history, with multiple descriptions by Galen and Hippocrates **(Aschoff AA et al .,1999)**. Despite the passage of more than two millennia from these early accounts, hydrocephalus remains a common, enigmatic, and challenging entity to treat. **(Hochstetler AA et al .,2022)**

Most modern surgical management strategies for obstructive and non-obstructive hydrocephalus have followed evolving cerebrospinal fluid (CSF) shunting strategies. However, recent advances in our understanding of hydrodynamic dysfunctions underlying hydrocephalus have spurred intervention strategies that focus on restoring normal physiologic CSF circulation rather than on external drainage. Neuroendoscopy, a vital tool in the minimally invasive paradigm, affords maximum access to the ventricular system**(Hochstetler AA et al .,2022)**

The cerebrospinal fluid circulates in a to-and-fro movement with a net caudal flow through the ventricles to the subarachnoid space **(Johanson CE et al .,2008).** The CSF flows unidirectionally from the lateral brain ventricles through the foramina of Monro, then through the third ventricle and the aqueduct of Sylvius into the fourth ventricle, and finally through the foramina of Luschka and Magendie into the subarachnoid space. The pumping action of the choroid plexus is believed to play a major role and that pulsation of the CSF is generated mainly by the filling and draining of the choroid plexuses. **(Bulat MA et al .,2011)**

Therefore, the CSF physiology conceived this way has been presented as the classical hypothesis of CSF hydrodynamics, i.e., CSF is actively produced (secreted) mainly from the choroid plexuses inside the brain ventricles, and then it circulates from the ventricles toward the subarachnoid space and is absorbed passively by the arachnoid villi into the venous sinuses . This means that in physiological conditions, the same CSF volume, which is actively formed by choroid plexus, must be passively absorbed into the cortical subarachnoid space. **(Bulat MA et al .,2011)**

An imbalance in this CSF production and absorption, leading to net accumulation of fluid and an enlargement of the brain ventricles, leads to hydrocephalus. The balance between production and absorption of CSF is critically important. The resulting pressure of the fluid against the brain tissue causing signs and symptoms of raised pressure is what constitutes hydrocephalus. **(Orešković DE et al ., 2017)**

Pathophysiology of Hydrocephalus :

It is easy to understand that, in theory, hydrocephalus can result from three mechanisms: increased resistance to cerebrospinal fluid flow, overproduction of cerebrospinal fluid, and increased venous sinus pressure. The consequence of all three mechanisms is an increase in cerebrospinal fluid pressure in order to maintain balanced secretion and resorption rates. The mechanisms responsible for ventricular dilatation are not fully understood. Ventricular dilatation may result from (1) a compression

of the cerebrovascular system, which is displaceable; (2) a redistribution of cerebrospinal fluid or extracellular fluid, or both, in the central nervous system; (3) a modification of the mechanical properties of the brain (increase in brain elasticity, alterations in the viscoelastic properties of brain, alteration of "brain turgor"); (4) the effect of the cerebrospinal fluid pulse pressure, which is still debated (some studies emphasize its importance as a causative factor in hydrocephalus, others suggest that it could be a contributory factor to ventricular expansion); (5) loss of brain substance, which in the long run contributes to the dilatation of the ventricles; and (6) in younger patients, an increase in skull volume due to the application of abnormal forces on functional cranial sutures. At this age, this additional volume is a major factor in the increase in cerebrospinal fluid **(Tamaki NA et al., 1990).**

A. An obstacle (obstruction) to cerebrospinal fluid flow:

Obstruction to cerebrospinal fluid flow is at the origin of most cases of hydrocephalus. The increased resistance caused by the obstacle leads to a proportional increase in cerebrospinal fluid pressure to keep resorption balanced. Hydrocephalus is usually classified according to the location of the blockage: whether it is in the ventricles or downstream from the ventricles, where it may be non-communicating or communicating, respectively. The site of the ventricular dilatation depends on the location of the blockage, which explains why hydrocephalus can also be described as biventricular, triventricular, or quadriventricular. The blockage can result from various pathologies: (1) malformations causing local narrowing of the cerebrospinal fluid pathways (e.g., aqueductal stenosis, Chiari malformation); (2) mass lesions leading to an intrinsic or extrinsic compression of the cerebrospinal fluid pathways (e.g., intraventricular tumor, paraventricular tumor, arachnoid cyst, hematoma); and (3) inflammatory processes (e.g., infections, hemorrhages) and diseases, such as mucopolysaccharidoses, inducing ependymal reactions, leptomeningeal fibrosis, and obliteration of arachnoid villi **(Lalou AD et al., 2018).**

B. Over secretion of CSF:

Cerebral fluid over-secretion results from choroids plexus papillomas or diffuse villous hyperplasia of the choroid plexus. However, choroid plexus papillomas and diffuse villous hyperplasia do not always cause hydrocephalus and hydrocephalus is not always relieved after excision of the tumor. According, the factors such as CSF pathway obstruction, arachnoiditis and inflammatory ependymitis have been put to explain the cause of hydrocephalus in these cases **(Sethi DE et al., 2017)**.

C. Increases in venous sinus pressure:

The increases in venous sinus pressure have a double consequence: (1) an increase in cortical venous pressure, leading to a larger intracranial vascular volume, and (2) an increase in intracranial pressure up to the level required to maintain cerebrospinal fluid flow against an abnormally high venous sinus pressure. The clinical consequences of this venous hypertension depend on skull compliance. If the cranial sutures are closed, the ventricular dilatation is counteracted by the concomitant increase in vascular volume. In this case, the raised venous pressure translates into the clinical picture of pseudotumor cerebri. Conversely, if the skull is compliant, abnormally increased intracranial pressure

leads to expansion of the cranium and, therefore, to an increase in fluid volume. This increase in venous sinus pressure can be of organic origin or functional origin (high-flow arteriovenous malformation) **(Tumani HS et al., 2017).**

Pathology of Hydrocephalus:

Regardless of the cause, obstruction of the CSF pathways results in a wide spectrum of pathologic findings that depend on the age of the patient, the expandability of the skull, and the type and duration of hydrocephalus **(Taheri AP, 2017)**.

Dilatation of the ventricular cavities is associated with ependymal alterations, a thin, stretched cortical mantle, and altered cerebral vascularization. As previously stated, the type of ventricular dilatation depends on the location of the blockage. Some characteristics are related to age. It seems that the mechanical properties of the immature cerebral parenchyma may favor the elective dilatation of the posterior part of the lateral ventricles. Two mechanisms have been proposed to explain this phenomenon: higher compliance of the posterior skull before fusion of the cranial sutures, and lesser distensibility of the anterior ventricular system surrounded by the compact gray matter structure of the basal ganglia **(Weller RA et al., 1993).**

The circulation of CSF in the subarachnoid space is frequently altered in hydrocephalus. In non-communicating hydrocephalus the subarachnoid fluid tends to flow normally towards the cerebral convexities. However, in other cases of non-communicating hydrocephalus, the convexities of subarachnoid space and/or basilar cisterns are mechanically obstructed by the enlarged ventricular system. Obstruction of the extra ventricular pathways probably accounts for the failure of third ventriculostomy on the treatment of some cases of non-communicating hydrocephalus **(Dubey AE et al ., 1997)**.

The overall incidence of hydrocephalus in the general population is not known. Since the condition occurs in association with a large number of childhood and adult intracranial diseases, it is obvious that the reported incidence of infantile hydrocephalus, namely 3 to 4 per 1000 live births, is grossly understated. The incidence of hydrocephalus occurring as a single congenital disorder is given as 0.9 to 1.9 per 1000 births, and that of hydrocephalus occurring with spina bifida and myelomeningocele varies from 1.3 to 2.9 per 1000 birth **(Vulcu SR et al., 2015)**.

Gliosis is a consistent finding in hydrocephalus, and inflammation and glial scar formation could play a major role in creating the chronic problems that plague hydrocephalic patients. It has been suggested by many investigators that scar formation is a permanent fixture in hydrocephalic brain**.(Mangano FT et al .,1998)**

It is likely that gliosis may dramatically change the mechanical properties of the brain so that it becomes more rigid (less compliant) and resistant to increases in CSF pressure and flow. Most recently, an interesting and potentially powerful relationship has been suggested between astrocytes and aquaporin (AQP) channels, which can have major impact on CSF absorption. **(Verkman AS et al .,2017)**

An important component of the pathophysiology of hydrocephalus is a change in intracranial compliance, which may lead to a redistribution of the pulsation dissipation mechanism (**Egnor MA et al .,2002).** Increased capillary pulsatility may have several pathophysiologic consequences. Structural responses may lead to the loss of parenchymal microvessels, and in fact, decreased capillary density has been shown in experimental hydrocephalus**. (Del Bigio MR .,2010)**

Increased intraventricular pressure and ventriculomegaly can cause secondary neurovascular damage and inflammation, creating an increase of tissue injury that further compromises brain development. **(Nagra GA et al .,2018)** .Acute ventriculomegaly results in compression and stretch of periventricular tissue (including axons, myelin, andmicrovessels) causing ischaemia, hypoxia, inflammation . Chronic ventriculomegaly elicits gliosis and chronic inflammation, demyelination, axonal degeneration, periventricular oedema, metabolic impairments, and changes to blood–brain barrier permeability. **(Nagra GA et al .,2018)**

Classifications of Hydrocephalus

Historically, hydrocephalus has been classified as *obstructive* or *nonobstructive*, a somewhat misleading classification because all forms of hydrocephalus, except hydrocephalus ex vacuo (resulting from brain atrophy), involve some form of CSF obstruction **(Rekate HL ., 2008)**.

In the earliest studies of the pathophysiology of hydrocephalus, **Dandy** and **Blackfan** in **1913*(*Dandy WE and Blackfan KD ., 1913*)*** classified hydrocephalus into two types: *communicating* and *non-communicating*. This classification was based on the injection of a Supravital dye into the lateral ventricle and its collection in the spinal subarachnoid space after a spinal tap **(***Quoted from* **Rekate HL , 2011).**

In 1960, **Ransohoff *(*Ransohoff JA et al ., 1960*)*** and coworkers recognized the basically obstructive nature of all hydrocephalus and proposed a new classification using the terms *intraventricular obstructive (non-communicating)* and *extra ventricular obstructive (communicating)* hydrocephalus **(***Quoted from* **Rekate HL , 2011).**

There are several other less commonly used classifications. Hydrocephalus can be divided into *physiologic*, i.e. secondary to CSF overproduction mainly from choroid plexus tumors, or *non-physiologic*. However, because such choroid plexus tumors are rare (less than 1% of all brain tumors), this classification has only minor clinical application. Another classification infrequently employed in the literature describes hydrocephalus as *internal* or *external*, depending on whether the site of obstruction is proximal or distal to the basal foramina. Hydrocephalus can also be classified by etiology and site of obstruction **(Rekate HL ., 2009)**..

Using the imaging modalities now available to neurosurgeons, classification of hydrocephalus should reflect the actual anatomic site of obstruction, because each site is associated with different causes and clinical syndromes **(Rekate HL ., 2004)**

Table (1): Classification of hydrocephalus (OI SA ., 2011)

Non-communicating hydrocephalus	Communicating hydrocephalus
I- Congenital lesions :	**I- Congenital lesions:**
A-Foramina of Monro : 1. Congenital atresia of both foramina. 2. Occlusion of one foramen by: ♦ Atresia ♦ Congenital membrane ♦ Gliosis	**A)** Arnold-chiari malformation **B)** Encephalocele **C)** Leptomeningeal inflammation **D)** Congenital absence of granulations
	II- Acquired lesions:
B- Aqueductal obstruction: 1.Gliosis. 2.Forking. 3.True narrowing. 4.Septum.	**A- Leptomeningeal inflammation** ♦ Infection. ♦ Hemorrhage. ♦ Particulate matter
C- Atresia of the foramina of Luschka and Magendie (Dandy Walker cyst).	**B- Masses:** ♦ Tumors. ♦ Non-neoplastic masses
D- Masses: 1. Benign intracranial cysts. 2. Vascular malformation. 3. Tumors.	**III- Over-secretion of CSF** **A-** Choroid plexus papilloma **B-** Choroid plexus hypertrophy
II- Acquired lesions:	
A- Aqueductal stenosis (gliosis). **B- Ventricular inflammations and scars** **C- Masses:** * Tumors * Non-neoplastic masses	

Etiologies of Hydrocephalus:

Hydrocephalus is the pathological condition caused by an abnormality of production or absorption of CSF in the brain. This disease is particularly common in infants and children. Hydrocephalus may be primary (idiopathic) or secondary (acquired), with the majority of congenital cases being idiopathic in origin. Common causes of secondary hydrocephalus in children include meningitis, trauma, brain tumors, intracranial hemorrhage, and developmental anomalies of the brain **(Gupta NA et al., 2007)**.

- **Congenital:**

A. Chiari Type I malformation: hydrocephalus may occur with 4th ventricle outlet obstruction.

B. Primary aqueductal stenosis (usually presents in infancy, rarely in adulthood)

C. Secondary aqueductal gliosis: due to intrauterine infection or germinal matrix hemorrhage.

D. Dandy- Walker malformation (atresia of foramina of Luschka & Magendie) the incidence of this in patients with hydrocephalus is 2.4%.

E. Rare X-linked inherited disorder **(Cinalli GA et al., 2012)**.

X-linked hydrocephalus **(Bickers-Adams syndrome)** is a well-defined, recessively transmitted disorder that accounts for roughly 7 per cent of cases of hydrocephalus in males. The condition is characterized by stenosis of the aqueduct of Sylvius and severe mental retardation. About half of affected children have an adduction-flexion deformity of the thumb. This syndrome can also exist without hydrocephalus **(Tully HM et al ., 2014).**

- **Acquired:**

A. Infectious (the most common cause of communicating hydrocephalus): Post-meningitis (especially purulent and basal, including TB) & Cysticercosis. **(Hailong FA et al .,2008)**

B-Post-hemorrhagic (2nd most common cause of communicating hydrocephalus)

- Post- subarachnoid hemorrhage.
- Post-intraventricular hemorrhage (IVH): many will develop transient hydrocephalus. 20-50% of patients with large intraventricular hemorrhage develop permanent hydrocephalus. **(Greitz DA , 2004)**

C-Secondary to Masses

- Non neoplastic: e.g. vascular malformation **(Greitz DA , 2004)**
- Neoplastic: most produce obstructive hydrocephalus by blocking CSF pathways, especially tumors around aqueduct, e.g. medulloblastoma. A colloid cyst can block CSF flow at the foramen of Monro. Pituitary tumor: suprasellar extension of tumor or expansion from pituitary apoplexy. **(Greitz DA , 2004)**

D-Post-operative: 20% of pediatric patients develop permanent hydrocephalus (requiring shunt) following posterior fossa tumor removal. May be delayed up to 1 yr

E- Neurosarcoidosis. **(Tully HM et al ., 2014).**

F-"Constitutional ventriculomegaly": asymptomatic. Needs no treatment **(Oi SA, 2011).**

G-Associated with spinal tumors **(Oi SA, 2011).**

Possible genetic origins

Genetic factors are funders to both syndromic and non syndromic forms (table 2).**(Stoll CE et al ., 1992) .** Population studies show familial aggregation of congenital hydrocephalus, with increased

recurrence risk ratios for same sex twins and first and second degree relatives. **(Munch TN et al .,2012)**

Most patients with non syndromic congenital hydrocephalus have aqueduct stenosis. **(Adle-Biassette HA et al .,2013)** Of these, X-linked hydrocephalus is the most common heritable form, accounting for about 10% of cases in boys (table 2).Together, human and animal molecular genetic data show that most hydrocephalus genes encode growth factors, receptors, cell-surface molecules (including cilia), and their associated intracellular signaling molecules that regulate brain growth and development**.(Zhang JA et al .,2006)**

E

	Putative genetic link
X-linked hydrocephalus with aqueduct stenosis (307000)	*L1CAM*
Non-syndromic autosomal recessive hydrocephalus (HYC; 236600 [HYC1]; 615219 [HYC2])	*CCDC88C; MPDZ*
Fried-type syndromic mental retardation (304340)	*AP1S2*
Walker-Warburg syndrome (multiple subtypes)	*POMT1; POMT2; POMGNT1;* and others
Neural tube defects (folate-sensitive [601634] and insensitive [182940] forms)	Multiple susceptibility genes involved in planar-cell polarity—eg, *FUZ, VANGL1/2, CCL2,* and others; folate-sensitive neural tube defects associated with genes in folate synthesis pathway (*MTR, MTRR, MTHFR, MTHFD*)
Primary ciliary dyskinesia's and other ciliopathies (including the many heterogeneous subtypes of Mekel-Gruber syndrome and Joubert syndrome)	Multiple genes involved in cilia structure, function, and regulation—eg, *CC2D2A, TMEM67, MKS1,* and others
RAS-opathies—eg, neurofibromatosis type 1, Noonan's syndrome, Costello's syndrome, cardio-facio-cutaneous syndrome	*NF1;* Ras-Raf-MEK-ERK pathway genes—eg, *KRAS, BRAF, PTPN11,* and others
VACTERL-H (association of vertebral, anal, cardiac, tracheoesophageal, renal, and limb anomalies plus hydrocephalus; 276950)	*PTEN*
X-linked VACTERL-H (300515)	*FANCB*

Numbers given are Online Mendelian Inheritance in Man (OMIM) identifiers.

Table (2): Genetic abnormalities associated with pediatric hydrocephalus **(Kahle KT et al., 2016)**

Types of Hydrocephalus:

- **Obstructive Hydrocephalus**

The traditional definition of obstructive hydrocephalus stems from work in 1914 by Dandy and Blackfan. It refers to obstruction of bulk CSF flow, leading to dilatation and isolation of the proximal ventricular system from the subarachnoid space. **(Dandy WE et al .,1914)**

Obstructive hydrocephalus includes forms of hydrocephalus in which a physical obstruction within the ventricular system, or its outlet from the brain, impedes CSF flow. The level of the obstruction can vary, and it can occur over the entire span of the ventricular system, from the foramen of Monro to the third ventricle, the cerebral aqueduct, the fourth ventricle, and its outlets. Notable common etiologies of obstructive hydrocephalus include congenital or acquired stenosis of the foramen of Monro or the aqueduct, obstruction by parasites causing conditions such as neurocysticercosis, or tumors and arachnoid cysts that cause compression due to direct mass effect. **(Greitz DA , 2004)**

The causes of obstruction are very variable and can be classified as acquired and congenital. Some acquired causes of obstruction are tumors (ventricular; e.g., frequently foramen of Monro, pineal region, posterior fossa), vascular (intraventricular hematoma, infarction, aneurysms, Vein of Galen aneurysm), infections (abscesses and/or granulomas, neurocysticercosis, ependymitis), arachnoid cysts, acquired aqueductal stenosis (adhesions following infection or hemorrhage), and supratentorial masses causing tentorial herniation. Congenital causes are: Monro foramen atrasia, aqueductal stenosis, Dandy-Walker syndrome (atresia of foramen of Magendie and foramina of Luschka), and Chiari malformation. **(Greitz DA , 2004)**

Communicating Hydrocephalus also known as nonobstructive hydrocephalus, has been described in terms of CSF malabsorption resulting from a diverse list of possible etiologies. This type of hydrocephalus encompasses all cases in which the flow of CSF is obstructed at a point distal to the outlet of CSF from the brain (i.e., the foramina of Luschka and Magendie). This can occur within the subarachnoid space or at the level of the arachnoid granulations. **(Hailong FA et al .,2008)**

Common causes of communicating hydrocephalus include infections, intracranial hemorrhage, and trauma that lead to scarring and adhesions within the subarachnoid space. Equally common are idiopathic and congenital cases—usually presenting in the pediatric population—and normal pressure hydrocephalus, which occurs in the aging adult. However, the differentiation between obstructive and communicating hydrocephalus is somewhat arbitrary. **(Hailong FA et al .,2008)**

The pathophysiology of communicating hydrocephalus is a matter of much debate, and no identifiable consensus currently exists.**(Greitz DA ,2007)** .The development of communicating hydrocephalus appears to be characterized by derangements of multiple intracranial physiologic variables, including cerebrospinal fluid (CSF) flow dynamics, microvascular pulsatility, and compliance of the subarachnoid space and vasculature, among others. A brief description of the prevailng theories follows. The conventional "bulk flow" theory of CSF flow dynamics asserts that CSF is produced in a certain location and absorbed in another location, and that CSF flow within the ventricles and subarachnoid space occurs due to small differences in pressure between the sites of CSF production and absorption. **(Katayama SA et al .,1993)**

Scarring of the arachnoid villi due to insidious inflammatory responses to infection, hemorrhage, trauma, or neoplastic spread were proposed to result in impaired absorption in these arachnoid villi and subsequent development of communicating hydrocephalus. **(Rabiu TB ,2010)**

Commonly Encountered Clinical Conditions

- **Infantile Post-hemorrhagic Hydrocephalus**

The incidence of IVH increases inversely with decreasing birth weight or EGA. In a study of infants born in the mid-1990s weighing less than 1500 g, 22% had IVH, and one-fourth of those infants had progressive ventricular dilation. However, onethird of those who survived required CSF diversion. **(Murphy BP et al 2002)**

The diagnosis of any GMH-IVH is made in 20-38% of preterm infants of <28 weeks gestational age and in 15% in infants between 28 and 32 weeks **(De Vries LS et al .,2001).** Severe IVH, grade III with or without a periventricular hemorrhagic infarction (PVHI) according to Volpe, is more common in infants with a gestation below 28 weeks. Two recent studies reported an incidence of severe intraventricular hemorrhage (IVH) around 10% in infants with a gestational age below 28 weeks' gestation. **(De Vries LS et al .,2001)**

The pathogenesis has been explained by intravascular and vascular factors, with fluctuations in cerebral blood flow playing an important role. The germinal matrix has been referred to as an "immature vascular rete" with primitive vessels that cannot be classified as arterioles, venules, or capillaries. The vessels are thin-walled, lack structural support and are metabolically active, and they are vulnerable to injury and hemorrhage, particularly when exposed to hypoxia and/or fluctuations in cerebral blood flow **(De Vries LS et al .,2001)**.

The hemorrhage can be confined to the germinal matrix (GMH, grade I), or disrupt the ependymal lining and extend into the lateral ventricle, and is then classified as a grade II when there is a small amount of blood in the lateral ventricle, or as a grade III when the ventricle is acutely dilated due to clot that fills more than 50% of the ventricle **(Yeo KT et al .,2019).**

In addition, there can be parenchymal involvement. A parenchymal hemorrhage used to be classified as a grade IV, but rather than extension of the IVH and rupture of the ependyma, we now understand that a GMH-IVH can result in impaired venous drainage of the medullary veins in the white matter with subsequent congestion and stasis of blood, and therewith rupturing of these vessels can be seen in a fan shaped leash. The parenchymal hemorrhage is now classified as a periventricular hemorrhagic infarction (PHVI) **(De Vries LS et al .,2001)**.

- **Post-infectious Hydrocephalus** TORCH infections (toxoplasma, others (varicella, HIV, syphilis), rubella, cytomegalovirus, and herpes simplex) are responsible for antenatal brain infections and may present with a wide range of consequences—from asymptomatic to having a fatal outcome. The parasites invade and destroy the ependyma of lateral ventricles, and the debris fall into the ventricle and cause obstruction of CSF flow pathway **(Olariu TR et al .,2011).**

The other widely accepted hypothesis is that the leptomeningeal inflammation is the main cause of hydrocephalus in such patients. In bacterial meningitis, neutrophil migration into the subarachnoid space follows bacterial invasion. The resultant purulent exudate tends to collect in the Rolandic and Sylvanian sulci over the cerebral hemispheres and in the basal cisterns, where the subarachnoid space is deepest and where, presumably, cerebrospinal fluid flow is most sluggish. The exudate interferes with absorption of cerebrospinal fluid by the arachnoid villi and may also cause obstructive hydrocephalus by obstructing the foramina of Luschka and Magendie. Typically, the obstruction occurs toward the end of the second week of the illness, when neutrophils begin to degenerate and fibroblasts proliferate in the exudate. **(Edmond KA et al .,2010)**

The inflammation of the choroid plexus and ependyma also leads to an overproduction of CSF in the acute phase of the illness. This also contributes to the hydrocephalus and raised intracranial pressure.

Fourth ventricular outlets may be blocked by the exudates or leptomeningeal scar tissue or when there is obstruction of the aqueduct either due to a strangulation of the brain stem by exudates or by a subependymal tuberculoma thereby resulting in hydrocephalus. **(Dastur DK et al .,1995).**

The criteria for post-infective hydrocephalus for infants are (1) infants born with normal-sized heads with subsequent development of hydrocephalus, (2) history of febrile illness after birth, and (3) CSF cytology and biochemistry suggestive of post-infection sequelae **(Chatterjee SA et al .,2011)**

The commonest cause of bacterial meningitis in patients over the age of 2 months is gram-negative encapsulated organisms either H. influenzae, N. meningitidis, or Str. pneumoniae. Escherichia coli is the most common infecting agent in neonatal meningitis**(Chatterjee SA et al .,2011)**

Bacteria may reach the CSF by one of the three major pathways: hematogenous spread from a contiguous structure or by direct implantation within the CSF. The main organisms involved are enteric gram-negative bacteria. These organisms are encapsulated and possess endotoxin which may facilitate the breakdown of the blood-brain barrier and then the entry of organisms into the brain, in addition to its direct neuronal damaging effect **(Chatterjee SA et al .,2011)**

- **Post-traumatic Hydrocephalus (PTH)**

Ventriculomegaly is common after severe TBI **(Poca MA et al .,2005) .** Post-traumatic ventricular dilation may have a wide range of etiological factors: starting from neuronal loss due to head trauma and possible secondary ischemic insults to obstruction of CSF circulation resulting in hydrocephalus. It is important to differentiate between posttraumatic hydrocephalus and gliosis. However, the diagnosis is not always easy **(Licata CR et al .,2001).**

PTH may develop acutely in the presence of subarachnoid hemorrhage. Aseptic meningitis may lead to occlusion of basal cisterns. Similarly, meningitis following head injury can lead to communicating hydrocephalus. Hydrocephalus may be seen acutely in the presence of intracerebral hematoma causing obstruction to CSF flow **(Modi NJ et al .,2016) .**

Typically, PTH develops in the post-acute phase of head injury, weeks or months later. Development of PTH is presumed to be due to subarachnoid hemorrhage. Subarachnoid spaces in patients after head injury and hydrocephalus are obliterated with fibrosis; ependymal destruction and presence of subependymal gliosis together with loss of white matter especially around the ventricles are other prominent findings **(Honeybul SA et al .,2012).**

The degree to which fibrosis and obliteration of the subarachnoid granulations/subarachnoid space are contributory in the late onset of PTH is unknown **(Modi NJ et al .,2016)**. Studies suggested that hydrocephalus following decompressive craniectomy may be related to a reduction in pulsatile CSF flow **(Kaen AA et al .,2010)**. The effect of the skull and dura on CSF hydrodynamics has been explored experimentally: the resistance to CSF outflow after craniectomy decreases two fold and brain compliance (expressed using the pressure–volume index, PVI) increases. **(Czosnyka MA et al .,1996)**

- **Congenital and neonatal hydrocephalus**

The pathophysiology of congenital hydrocephalus almost always includes two separate mechanisms: primary genetic abnormalities that may affect outcome individually and secondary injury mechanisms that occur mainly as a result of expanding ventricles and/or altered CSF physiology . Forty percent of hydrocephalus cases are estimated to have possible genetic etiology **.(Zhang JR et al .,2006)**

X-linked hydrocephalus (HSAS1, OMIM) comprises approximately 5–15% of the congenital cases with a genetic cause **(Kuzniecky RI et al .,1986)** . L1CAM (L1 protein) at Xq28 has been implicated in X-linked human congenital hydrocephalus **(Katsuragi SA et al .,2000).** Recently, an X-linked adult-onset NPH and a form of familial NPH that is transmitted in autosomal dominant fashion **(Portenoy RK et al .,1984)**

X-linked hydrocephalus **(Bickers-Adams syndrome)** is a well-defined, recessively transmitted disorder that accounts for roughly 7 per cent of cases of hydrocephalus in males. The condition is characterized by stenosis of the aqueduct of Sylvius and severe mental retardation. About half of affected children have an adduction-flexion deformity of the thumb. This syndrome can also exist without hydrocephalus ***(Sainte-Rose CA , 1996)***

- **Loculated hydrocephalus or complex hydrocephalus**

Hydrocephalus arising from intraventricular septations is known as complex or loculated hydrocephalus. Many synonyms for complex hydrocephalus have been used in the literature such as compartmentalized or loculated hydrocephalus. **(Akbari SH et al .,2015)**

Complex hydrocephalus remains a challenging neurosurgical problem. Definitive treatment is surgical, yet the approach remains controversial. Traditional treatment consisted of shunting, often requiring the placement of multiple shunt systems and multiple revisions **(Akbari SH et al .,2015)**

Complex hydrocephalus is classified as either uniloculated or multiloculated. Uniloculated hydrocephalus means the presence of a single cyst inside the ventricular system, whether supratentorial (isolated lateral ventricle) or infratentorial (isolated fourth ventricle). Multiloculated hydrocephalus means the presence of multiple cysts or locules isolated by multiple intraventricular septations. Uniloculated hydrocephalus is generally congenital with unaffected cerebrospinal fluid pathways, whereas multiloculated hydrocephalus is generally postinfectious or postinflammatory with obliterated subarachnoid spaces. (**ElGhandour NM ., 2008)**

The distinction between both types is important because their pathogenesis, success of treatment and prognosis markedly differ. Consequently, it has been concluded that the 2 divergent types of complicated hydrocephalus should not be included in a single study . **(ElGhandour NM., 2008)**

Using the classification proposed by Spennato et al., the following variations can be distinguished: 1) hydrocephalus with multiple intraventricular septations; 2) isolated lateral ventricle/unilateral hydrocephalus; 3) entrapped temporal horn; 4) isolated fourth ventricle; and 5) expanding cavum septi pellucidi/cavum vergae. **(Spennato PA et al .,2007)**

The incidence and prevalence of multiloculated hydrocephalus are increasing probably due to increasing survival rates of children and neonates who suffered intraventricular hemorrhage and meningitis **(Oi SA et al .,1999)** .Shunt infection remains to be one of the most frequent causes of such serious disease. Therefore, every effort should be done to avoid shunt infection **(Fritsch MJ et al .,2002)**.

There is no international consensus about the incidence of multiloculated hydrocephalus; the incidences vary between 7 and 30% or more. Lorber and Pickering **(Lorber JA et al .,1966)** estimated the incidence of multiloculated hydrocephalus in cases of meningitis to be more than 30% **(Etus VA et al .,2016)** . However, Reinprecht et al. reported a long-term follow-up of posthemorrhagic hydrocephalus infants and revealed that intraventricular septations occurred only in 7% of cases **(Reinprecht AA et al .,2001)**

The definite pathophysiology of multiloculated hydrocephalus is not very well understood. Therefore, we carried out a study to understand, reveal, document the different stages of septum formation, and confirm the progressive nature of intraventricular septae (multiloculated hydrocephalus) showed collagenous fibrosis **(Andresen MA et al .,2012).**

The meninges also showed collagenous fibrosis or inflammation with fibrin deposition and infiltration by mononuclear inflammatory cells (lymphocytes, plasma cells) and neutrophils .At the final stage, CT and MRI show dilatation and loss of configurations of the ventricles. Progressive brain atrophy is common as brain melts out and is replaced by multiple cysts, and this is likely irreversible. Sometimes it is difficult to differentiate between ventricles and periventricular cysts **(Jamjoom AB et al .,1996).**

The stages of formation of multiloculated hydrocephalus and septum formation can be summarized in four stages which are: **Stage 1**: Formation of fibrinous, intraventricular membranes **Stage 2**: Increasing infiltration of membranes by inflammatory cells (lymphocytes sometimes accompanied by plasma cells and foamy histiocytes) **Stage 3**: Gliosis and early (perivascular) fibrosis of membranes **Stage 4**: Diffuse collagenous fibrosis of membranes with eventual transformation of membranes into dense, fibrotic septa with softening of the brain, loss of integrity, ventricular dilatation, and low ICP Intraventricular septae can be congenital or acquired and can be true or false septa. These septations will lead to the development of multiloculated hydrocephalus. **(Ammar AA et al .,2017)**

The timing of the start of development of ventricular septations varies with an average of 2–4 months following ventriculitis .The combination of bacterial infection especially gram-negative and intraventricular hemorrhage will lead to the most severe form of multiloculated hydrocephalus. Intraventricular septations occur as a result of fibrous adhesions developing within the ventricles and may contribute to the development of multiloculated hydrocephalus. **(Kalsbeck JE et al 1980)**

Meningitis is frequently associated with purulent ventriculitis. They also observed that it causes an inflammatory response in the ependyma with patchy or diffuse denudation of this cell layer and development of subjacent gliosis and gliotic tufts at the sites of ependymal disruption. They state further that glial tufts frequently projected into the exudate from the subependymal tissue **(Andresen MA et al .,2012).**.

The ventricular system may become trabeculated or encysted following bacterial meningitis or germinal matrix hemorrhage **(Andresen MA et al .,2012)**. Predisposing factors include a low birth weight, premature birth, perinatal complications and congenital central nervous system malformations **(Zuccaro GA et al ., 2011)**.

Septations can be true or pseudo septae depending on the origin either in the ventricles or in periventricular territories that later become ventriculized. These need to be observed early during their formation because later they cannot be differentiated. True septa may span the ventricular walls or float in the lumen. They can be delicate or coarse and resemble cobwebs or thin veils. They may be rather complex, occupying the entire ventricle, or focal with only solitary strands noted . **(Andresen MA et al .,2012).**.

Macroscopically , the membranes are completely extending through the ventricle to the other end or incompletely extending to part of the lumen . The membranes may be transparent, thin, and avascular; on the other hand, they may be thick and highly vascularized. Microscopically the septations are membranes composed of fibroglial tissues and round and polymorphonuclear cells. Features of chronic ventriculitis usually present in the form of subependymal gliosis, glial tufts extending through the destructed ependyma into the ventricular lumen. **(Spennato PA et al .,2007)**

Multiloculated hydrocephalus is considered so far, to be one of the diseases with unfavorable prognosis due to the progressive nature of the disease. There is hope in the future to stop the progression of this disease by using pharmacological agents to inhibit the underlying inflammatory pathogenesis of this disease. However, there is a need for preclinical and clinical trials to prove the efficacy and safety of this new modality of management. **(Ammar AA et al .,2017)**

The prognosis of multiloculated hydrocephalus depends on the extent of intraventricular septations, the surgical procedure done, and the presence or absence of previous neurological insults and morbidities. The outcome is evaluated by the A. Ammar et al. following: (1) the incidence of improvement of hydrocephalus in postoperative MR imaging (2) avoiding or eliminating the need for shunting, (3) simplifying complex shunt system, and (4) reducing shunt revision rate. **(Ammar AA et al .,2017)**

The early discovery of shunt complication, meningitis, and IVH may help to reduce the risk of such serious disease. Once the disease is diagnosed, aggressive antibiotic treatment, which may include intrathecal antibiotic injection, and daily washing the ventricles may help to abort the progressive sequale of the disease**(Ammar AA et al .,2017)**

No Conflict of interest.

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