Scientific Research Publishing

Open Journal of Pediatrics, 2025, 15(1), 21-37
https://www.scirp.org/journal/ojped
ISSN Online: 2160-8776
ISSN Print: 2160-8741

A Comprehensive Review of Pediatric Hydrocephalus

Lakshmi C. Devarapalli, Kelley J. Williams, Terry L. Oroszi

Department of Pharmacology & Toxicology, Boonshoft School of Medicine, Wright State University, Fairborn, USA
Email: terry.oroszi@wright.edu

How to cite this paper: Devarapalli, L.C., Williams, K.J. and Oroszi, T.L. (2025) A Comprehensive Review of Pediatric Hydrocephalus. *Open Journal of Pediatrics*, **15**, 21-37.
https://doi.org/10.4236/ojped.2025.151003

Received: March 20, 2024
Accepted: January 3, 2025
Published: January 6, 2025

Copyright © 2025 by author(s) and Scientific Research Publishing Inc.
This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).
http://creativecommons.org/licenses/by/4.0/

Open Access

Abstract

Hydrocephalus is a medical condition caused by an abnormal cerebrospinal fluid (CSF) buildup in the brain's ventricles. This excess fluid causes the ventricles to enlarge, increasing pressure within the brain. CSF typically flows through the ventricles and around the spinal column, bathing the brain. However, the increased pressure from excess CSF associated with hydrocephalus can damage brain tissue and lead to various problems with cognitive function. While it can occur at any age, hydrocephalus is the most common in infants and adults over 60. It has been a subject of fascination for physicians throughout history due to its striking presentation. Two main types of hydrocephalus exist: obstructive (noncommunicating) and communicating. A blockage in the CSF flow causes obstructive hydrocephalus, while communicating hydrocephalus occurs when the body's ability to absorb CSF is impaired. The review delves into the intricacies of hydrocephalus, exploring its causes, symptoms, and pathophysiology. The latest research on the topic has been examined, including innovative treatment approaches and ongoing challenges in managing this complex condition.

Keywords

Hydrocephalus, CSF, Ventricles, Pathogenesis, Pediatric

1. Introduction

Across all vertebrate animals and the majority of invertebrates, the brain continues to serve as the hub of the nervous system. It is located within the head, typically close to the sensory structures that support senses, such as vision. This is the most intricate organ that is part of a vertebrate. The human brain seems to be the nervous system's command center, enabling ideas, processing thoughts and feelings, and memory, and it is involved with movement and emotions through a

complex function that represents the highest outcome of evolutionary processes and biological responses [1].

Maintaining robust brain health throughout life is crucial for longevity and overall well-being, especially as the global population ages and the prevalence of neurological disorders rises. The brain, the central command center of the nervous system in vertebrates and most invertebrates, is a complex organ with distinct regions. The forebrain, the largest region, comprises the cerebral hemispheres, corpus callosum, thalamus, hypothalamus, and hippocampus. Located beneath the forebrain is the hindbrain, consisting of the cerebellum, pons, and medulla [2].

Hydrocephalus is a significant neurological condition that has intrigued physicians for centuries due to its complex presentation and impact on cognitive function. This review aims to provide a comprehensive overview of pediatric hydrocephalus, examining its causes, symptoms, and pathophysiology. The study also highlights the latest research and innovative treatment approaches, addressing the ongoing challenges in managing this condition [3] [4].

2. Historical Overview of Hydrocephalus

Hydrocephalus has been recognized and studied throughout history, with significant contributions from various medical pioneers. Their work has laid the foundation for our current understanding and treatment of this condition [5].

2.1. Early Recognition and Understanding

Hippocrates (460-377 BC) was one of the earliest physicians to recognize and describe hydrocephalus, noting its clinical presentation and suggesting treatments like depressurization.

Claudius Galen (130-200 AD) furthered the understanding of hydrocephalus by recognizing the role of vasodilation in intracranial compartments.

2.2. Advances in Anatomy and CSF Dynamics

Thomas Willis (1621-1675) made significant contributions to understanding the ventricular system and cerebrospinal fluid (CSF) pathways, laying the groundwork for further research on hydrocephalus.

Franciscus Sylvius (1614-1672), Alexander Monroe (1733-1817), and Francois Magendie (1783-1855) provided crucial details about the anatomy of the CSF pathway, essential for comprehending the dynamics of hydrocephalus.

Key and Retzius (1876) established the modern concept of CSF circulation, a cornerstone of hydrocephalus diagnosis and treatment.

2.3. Innovations in Surgical Treatment

Walter Dandy (1922) introduced the concept of third ventriculostomy, a surgical procedure that remains relevant today for treating obstructive hydrocephalus.

Mixter (1950s) pioneered techniques for endoscopic third ventriculostomy, revolutionizing the surgical approach to hydrocephalus and improving patient

outcomes.

The collective efforts of these and many other researchers have transformed the landscape of hydrocephalus care. Their contributions have enabled earlier diagnosis, more effective treatments, and improved quality of life for countless individuals affected by this condition. See Table 1 for a summary of key historical contributors [6] [7].

Table 1. Key historical figures and their contributions to hydrocephalus.

Figure	Time	Contribution
Hippocrates	460-377 BC	Recognized the condition and described its symptoms.
Claudius Galen	130-200 AD	Acknowledged vasodilation in intracranial compartments.
Thomas Willis	1621-1675	Advanced understanding of the ventricular system and CSF pathways.
Franciscus Sylvius	1614-1672	Contributed to the anatomy of the CSF pathway.
Alexander Monroe	1733-1817	Furthered the anatomical knowledge of the CSF pathway.
Francois Magendie	1783-1855	Made significant contributions to the anatomy of the CSF pathway.
Key and Retzius	1876	Established the modern concept of CSF circulation.
Walter Dandy	1922	Suggested third ventriculostomy for obstructive diseases.
John Scarff	1963	Provided an in-depth historical account of hydrocephalus diagnosis.
Mixter	1950s	Developed endoscopic third ventriculostomy techniques.

3. Embryology

The ventricular system develops from the corresponding vesicles of the neural tube. Therefore, the cavity of every telencephalic vesicle has now become the lateral ventricle, and the cavity of the diencephalic vesicle's cavity becomes the third ventricle. The fourth ventricle is formed by the cavity of the rhombencephalon [8]. The central canal continues into the spinal cord. Thus, every lateral ventricle is a spherical space within the telencephalic vesicle throughout development. The ventricle grows Antero posteriorly as it grows forward and backward. The posterior end tends to grow downward and forward to establish the chronological horns, giving the ventricles a "C" shape. Finally, the occipital horns recede. The convergence of the two emerging telencephalic vesicles causes these same medial walls of the lateral ventricles to collide, forming a septum [9]. Well, this surface develops into the third ventricle's roof, as well as its lateral invagination creates a choroidal fissure. The tela choroidea is created by extending a mater fold of the pia into this fissure. A collection of capillaries grows in this fold, creating the choroid plexus [4] [10]. Table 2 outlines the stages of ventricular system development and their relationship to hydrocephalus.

Table 2. Stages of ventricular system development and their relationship to hydrocephalus.

Step	Description	Relation to Hydrocephalus
Neural Tube Formation	Around the third week of gestation, the embryo's ectoderm folds inward, forming the neural groove. The edges of this groove fuse, creating the neural tube, the precursor to the central nervous system (brain and spinal cord).	Disruptions during neural tube formation can lead to congenital malformations, including neural tube defects that may contribute to the development of hydrocephalus.
Primary Vesicles	The neural tube initially expands into three primary vesicles: the prosencephalon (forebrain), mesencephalon (midbrain), and rhombencephalon (hindbrain).	Abnormal development of these primary vesicles can result in structural anomalies that obstruct CSF flow, potentially leading to hydrocephalus.
Secondary Vesicles	By the fifth week, the prosencephalon further divides into the telencephalon and diencephalon, while the rhombencephalon divides into the metencephalon and myelencephalon. These secondary vesicles give rise to various brain structures.	Improper division or growth of these secondary vesicles can cause malformations in the brain's ventricular system, increasing the risk of hydrocephalus due to impaired CSF circulation.
Ventricular System Development	The central cavity within the neural tube develops into the ventricular system: • The telencephalon gives rise to the lateral ventricles. • The diencephalon forms the third ventricle. • The mesencephalon narrows to become the cerebral aqueduct, connecting the third and fourth ventricles. • The metencephalon and myelencephalon contribute to the fourth ventricle.	Any disruptions in the development of the ventricular system can lead to blockages or narrowing of pathways (e.g., cerebral aqueduct), resulting in obstructive hydrocephalus.
Choroid Plexus Formation	Around the sixth week, specialized cells within the ventricles differentiate to form the choroid plexus. This vascular structure is responsible for producing cerebrospinal fluid (CSF).	Abnormalities in the formation of the choroid plexus can lead to overproduction or underproduction of CSF, contributing to the development of hydrocephalus.
CSF Circulation	By the end of the first trimester, the ventricular system is established, and CSF begins to circulate through the ventricles, subarachnoid space, and central canal of the spinal cord.	Impaired CSF circulation due to structural anomalies or blockages can result in the accumulation of CSF, leading to increased intracranial pressure and hydrocephalus.

4. Classification

The precise site of the CSF flow obstruction can be determined using CT and magnetic resonance imaging (MRI) techniques. Consequently, the following classification is more accurate: One of three things can lead to hydrocephalus:

1) An excessive amount of CSF is produced (a rare condition).

2) The lateral ventricles and foramen of Monroe, the aqueduct of Sylvius, the third and fourth ventricles, or the subarachnoid spaces are blocked from CSF flow.

3) Defects in the absorption.

Hydrocephalus is a complex neurological condition characterized by an abnormal cerebrospinal fluid (CSF) accumulation within the brain's ventricles [11]-[13]. Hydrocephalus is managed by a buildup of fluid inside the ventricles, which are deep inside the brain. Extra fluid causes the ventricles to expand, increasing the amount of pressure in the brain [14]. Typically, cerebral spinal fluid bathes the spinal column in the brain by passing through into the ventricles. However, the pressure of too much cerebrospinal fluid associated with hydrocephalus can damage brain tissues and cause a variety of cognitive function problems. While the most common types of hydrocephalus are obstructive (noncommunicating) and communicating, other classifications are based on specific criteria. One classification system categorizes hydrocephalus based on the number of ventricles involved. Monoventricular hydrocephalus affects only one lateral ventricle, while biventricular hydrocephalus involves both lateral ventricles. Triventricular hydrocephalus affects both lateral and third ventricles, and panventricular hydrocephalus involves all four ventricles.

Another classification system categorizes hydrocephalus based on its cause. Congenital hydrocephalus is present at birth, while acquired hydrocephalus develops after birth due to various factors such as injury, infection, or tumor. Idiopathic hydrocephalus is diagnosed when the cause cannot be determined.

Other types of hydrocephalus include normal pressure hydrocephalus (NPH), which primarily affects older adults and is characterized by a triad of symptoms: gait disturbance, dementia, and urinary incontinence. Hydrocephalus ex-vacuo occurs when brain tissue is lost, leading to an apparent increase in CSF volume [15]. A secondary classification under one of the following headings may be added, depending on the precise etiology: Neoplastic, traumatic, degenerative, congenital, inflammatory, and other types of hydrocephalus.

Although hydrocephalus can appear at any age, it is more common in infants and people 60 years and older. Since its inception, doctors have been fascinated by hydrocephaly due to its horrifying appearance [16]. Procedures that provide more effective treatment will have to be created once the anatomy and pathophysiology of hydrocephalus, as well as the production and absorption of cerebrospinal fluid, have been clarified.

There are obstructive and non-obstructive subtypes of hydrocephalus [17]. It is known that either a CSF flow obstruction or a decrease in the body's capacity to store CSF can lead to hydrocephalus. The pressures within the brain then rise by

swelling brought on by CSF buildup inside the ventricles and subarachnoid spaces. Despite the likelihood of intracranial hypertension in children over the age of two, infants frequently develop progressive macrocephaly [18]. Traditional methods that incorporate abnormal cerebral pulsations, brain compliance, and unique, fully categorized water transport mechanisms are replacing the conventional theory of hydrocephalus as the result of a blockage inside the bulk flow of the CSF.

Several causes of hydrocephalus develop when the balance between CSF production and absorption is disturbed, leading to dilated ventricles. There seem to be numerous classifications; however, the two most used are obstructive (non-communicating) and communicating. The obstructive pathway manifests as a block in cerebrospinal fluid (CSF) proximal to arachnoid granulation, whereas the direct pathway method manifests itself as an abnormality in uptake in arachnoid granulation [19].

5. Signs and Symptoms

Depending on the person's age, stage of the disease, and level of acceptance of the situation, the hydrocephalus of each person will manifest differently clinically.

Adults may experience loss of function, such as difficulty walking or thinking, while infants and young children may be more susceptible to symptoms of increased intracranial pressure, such as vomiting. An infant's ability to compensate for increased CSF pressure and ventricle enlargement differs from an adult. The infant skull may enlarge to facilitate the accumulation of CSF because the sutures, the fibrous joints connecting the skull bones, have not yet been forced to close [20] (**Table 3**).

Table 3. Hydrocephalus symptoms manifest differently across various age groups.

Age Group	Symptoms
Infants/Neonates	Scalp veins
	Downward deviation of the eyes (also called "sunset")
	Vomiting
	Irritability
	Sleepiness
	Seizures
	Rapidly increasing head circumference
Children	Blurred or double vision
	Lethargy
	Nausea
	Headache
	Sun setting of the eyes
	Problems with balance walking
	Poor coordination
	Vomiting
	Drowsiness
Adults	Loss of function, such as difficulty walking or thinking
	Blurred or double vision

Continued

	Lethargy
	Nausea
	Headache
	Sun setting of the eyes
	Problems with balance walking
	Poor coordination
	Vomiting
	Drowsiness

6. Risk Factors

Hydrocephalus is a complex condition with a multifactorial etiology. While the exact causes of hydrocephalus are not always clear, research suggests a possible link between comorbidities, environmental factors, and the development of hydrocephalus, particularly in pediatric cases. Comorbidities, or coexisting medical conditions, can play a significant role in the development of hydrocephalus. For instance, maternal diabetes has been associated with an increased risk of congenital abnormalities and growth deformities in infants, including hydrocephalus. This may be due to a more permeable blood-brain barrier in mothers with diabetes, potentially leading to increased CSF production and brain disorders such as hydrocephalus.

Similarly, maternal hypertension during pregnancy has been linked to hydrocephalus in some children. This may be due to decreased placental blood flow, resulting in reduced oxygen and nutrient supply to the fetus, potentially contributing to the development of hydrocephalus. Environmental factors can also interact with comorbidities to increase the risk of hydrocephalus. For example, socioeconomic factors, such as poverty and malnutrition during pregnancy, can contribute to fetal growth retardation and central nervous system malformations, including hydrocephalus. Furthermore, exposure to certain environmental toxins or infections during pregnancy can also increase the risk of hydrocephalus in the developing fetus. The complex interplay between comorbidities and environmental factors highlights the multifactorial nature of hydrocephalus. Further research is needed to fully understand these intricate relationships and develop effective prevention and treatment strategies.

The most typical risk factors include**:** [21]-[23]

- Lack of prenatal care
- Maternal diabetes
- Maternal chronic hypertension
- Maternal hypertension during gestation
- Lifestyle issues
- Malnourished during pregnancy

An abnormal buildup of cerebrospinal fluid in the cerebral ventricles is known as hydrocephalus, and it is typically caused by a problem with the fluid's bloodstream absorption. In other words, when the CSF cannot travel adequately from its point of production inside the cerebral ventricles toward its point of absorption

into the systemic circulation, it causes hydrocephalus, an active distension of the brain's ventricular system.

Although patients with this disorder have a less-than-ideal prognosis, the pathophysiology of congenital and neonatal hydrocephalus is not well understood. This could be because the injury mechanisms are numerous and overlap with epidemiology, which is also complex and varied [24]. Mechanical, ischemic, and metabolic-toxic disturbances are their main mediators [25]. iNPH combines several pathogenetic elements, creating a vicious cycle that reinforces itself. Most studies suggest CSF disturbances due to altered hemodynamics [26]. Vascular, hemodynamic, and metabolic factors are all part of the physiopathology of iNPH.

- Most of the time, the disease starts with CSF disturbances.
- Hakim's triad can be explained by cerebral dyshomeostasis, hypometabolism, and neurotoxicity.
- In iNPH, neurodegeneration is more of a side effect than a pathogenetic factor.
- Before delving into the pathogenesis of NPH, it is important to comprehend the production, circulation, and absorption of CSF and their ranges.

7. CSF Dynamics

It is generally accepted that the choroid plexuses, which account for 70% to 80% of CSF production, are the primary sites of CSF production. Here, CSF is filtered from across capillaries' endothelial walls and secreted through the choroidal epithelium. Since CSF formation of CSF is thought to be an active process independent of intracranial pressure, hydrocephalus will result from a blockage of the CSF pathways [27]. The following is the typical pathway for CSF from production to clearance: The cerebral spinal fluid (CSF) leaves the choroid plexus. It travels through the lateral ventricle, interventricular foramen of Monroe, third ventricle, cerebral aqueduct of Sylvius, fourth ventricle, two lateral foramen of Luschka, one medial foramen of Magendie, subarachnoid space, arachnoid granulations, Dural sinus, and ultimately venous drainage. The Dural sinus, the subarachnoid space, the arachnoid granulations, two medial foramina of Luschka, yet another medial foramen of Magendie, and eventually the venous drainage [28].

7.1. Circulation of the Cerebrospinal Fluid

The pulsatile pumping action of the choroid plexuses, produced by the filling or draining into choroid plexuses, is believed to be what causes the flow of CSF [29]. The CSF is pushed out of the ventricles and into the SAS by each pulse of the choroid plexus. Furthermore, there is a certain flow of CSF into the spinal SAS, presumably at a lower intensity [30].

7.2. CSF Absorption

The arachnoid villi of the Dural venous sinuses have long been believed to serve as the primary site of CSF absorption. According to a hydrostatic gradient, CSF is believed to be passively consumed from the cranial SAS to the cranial venous

blood [31]. The villi in the arachnoid granulation were originally defined as an open tubular system that protruded into the venous sinus from the granulation tissue. Ultrastructural studies have not consistently supported these pressure-sensitive openings through the arachnoid villi.

7.3. Ranges of CSF

0.20 - 0.35 ml/min of CSF are produced normally; the choroid plexus, located primarily in the lateral and fourth ventricles of the ventricular system, is responsible for producing most of this fluid. In a healthy individual, the lateral and third ventricles each have a capacity of 20 ml. An adult's CSF contains 120 ml in total [32].

There are several theories and hypotheses to explain the pathogenesis of iNPH,

- The CSF cannot pass through the ventricular wall.
- Ventricular CSF seeps into the parenchyma, where it is effectively absorbed.
- Ventricular CSF seeps into the parenchyma but is ineffectively absorbed.

There are three main categories when it comes to hypotheses. The first is circulation theory, a widely accepted theory for the emergence of hydrocephalus, but itacks sufficient support in clinical and experimental contexts [33]. However, there is substantial evidence that osmotic gradients, also present in these other water-permeable organs of the body, are responsible for the water content of the brain ventricles [34]. Consequently, changes in the osmotic gradient and hydrocephalus result from brain disorders that produce too many macromolecules in the ventricular CSF. There is only a slight connection between the theory of macromolecules and osmatic gradients [35].

As osmotic gradients play an important role in water transport into the ventricles, the transport of osmotically active macromolecules plays a critical role in the genesis of hydrocephalus [36]. Current evidence points to paravascular and/or lymphatic clearance of these macromolecules from the ventricles and the brain into the venous system. Therefore, we can view hydrocephalus as a disorder of macromolecular clearance, rather than circulation.

8. Pathogenesis of Hydrocephalus

The following are the theories that explain the pathogenesis of hydrocephalus:

- Circulatory Theory
- Osmatic Gradients
- Macromolecular Clearance
- Supportive Theory

8.1. Circulatory Theory

Circulation theory states that CSF is actively produced from choroid plexuses in the ventricles and flows from the lateral ventricles through the Monroe foramen, the third ventricle, the aqueduct, the fourth ventricle, and then through the Luschka and Magendie into the subarachnoid space (SAS), where it is passively absorbed into cranial venous sinuses into the blood [37]. Circulation theory was

proposed a century ago and is based on three key premises the active formation or secretion of CSF, the passive absorption of CSF, and the unidirectional flow of CSF from the place of formation to the place of absorption. These premises led to the description of the CSF circulation as the third circulation (after blood and lymphatic circulations) [38] [39].

The Particulars Supporting Circulatory Theory

The theory stating that the choroid plexus is the main source of CSF formation is further challenged by the observation that the volume and composition of CSF do not change when the choroid plexuses have been removed. Dandy and Black fan [7] were the first to induce experimental hydrocephalus by obstructing the aqueduct in a dog using a cotton pledge in a capsule. Aqueductal stenosis has been associated with hydrocephalus and is considered causative and has been shown to follow hydrocephalus development in animal models [40] and humans [41]. First, aqueductal obstruction without induced inflammation did not result in dilation of ventricles or even increased pressure compared to control animals [42]. Second, there is no evidence to pinpoint the routes the CSF takes from the choroid plexus in the lateral ventricles through the aqueduct. Fenstermacher showed that 14Csucrose, when injected into the lateral ventricles, moves into the third ventricle and the basal cisterns through the roof of the third ventricle before entering the aqueduct. If obstructions in the CSF pathways drive the development of hydrocephalus, there should be a corresponding change in the trans mantle pressure gradients. The trans mantle pressure gradient is the difference between the intraventricular pressure and the pressure in the SAS. This gradient has been hypothesized to be the driving force of ventricular dilation.

8.2. Osmatic Gradient Theory of Pathogenesis

One of the fundamental presumptions of circulation theory is that the brain parenchyma is immune to CSF and unable to absorb the CSF that builds up in the ventricles. However, water can pass through the brain parenchyma. The specific ion channels that allow water to move with ions and aquaporin channels that permit water to flow freely without affecting the ionic environment make up the molecular basis of this permeability. Membrane proteins known as aquaporin channels permit water movement but not ions. Both the ends of the astrocyte and the ependymal cells that line the lateral ventricles contain aquaporin 4 (AQP4) channels. These astrocytes specifically contact micro-vessels in the cerebral cortex's periventricular white matter and subpial periventricular cortex.

Osmotic gradients affect the pathogenesis of hydrocephalus. Except for the ventricular space, osmotic gradients are known to affect brain tissues in both normal and abnormal states based on clinical signs. Osmotic diuretics, such as mannitol, are administered intravenously in the case of brain edema to remove water from the brain's extracellular space. Hyponatremia can cause brain swelling by allowing water to permeate into the brain tissues and cause cerebrovascular edema [28].

Water is transported into the compartment from the blood. When hydrocephalus is identified, those that accumulate on the membrane's outer edge are the main reason for the elevated protein levels in the CSF fluid. Higher concentrations of thrombopoietin, ferritin, chondroitin sulfate proteoglycan, transforming growth factor beta 1, vascular endothelial growth, and transforming growth factor beta two were found in the ventricular CSF of patients with intraventricular hemorrhage-induced hydrocephalus [42].

Experimental studies have shown that infusing hyperosmolar dextran into the cerebral ventricles alters the osmotic gradient, resulting in hydrocephalus throughout. Furthermore, the consequence of hydrocephalus increases in direct correlation with an increase in osmotic load in the ventricles. Other researchers have also affirmed that osmotic gradients play a role in the development of hydrocephalus (90 - 92). These findings imply that water transport further into the right ventricle is unrelated to the osmotic load or the number of macromolecules present.

8.3. Macromolecular Clearance

Paravascular and lymphatic pathways are the underlying mechanisms that help with the clearance of macromolecules. Macromolecules infused into the ventricles are cleared through the brain parenchyma along the perivascular spaces and the cribriform plate into the nose [43]. These findings show that macromolecules infused into the ventricles or intrathecal spaces are distributed in paravascular pathways, also termed glymphatic pathways or systems. Injected particulate matter is rapidly and efficiently ingested by perivascular cells. The authors summarized these findings in a review article, highlighting Para vascular and nasal lymphatic pathways and their immunological significance. The authors proposed that this absorption of macromolecules by immunologically competent cells be an explanation for immune-mediated CNS disorders. The exact mechanism of macromolecular clearance outside the brain is uncertain [44].

8.4. Supportive Theory

Supportive therapy for hydrocephalus in children may include the use of diuretics like carbonic anhydrase inhibitors and loop diuretics. Diuretics are known to have important therapeutic efficacy in the treatment of hydrocephalus.

Hydrocephalus is a complex condition caused by several different disorders. Circulation theory, while widely accepted as representative of how hydrocephalus develops, lacks adequate evidence in clinical or experimental settings. There is strong evidence that osmotic gradients, like those found in other water-permeable organs, have become willing to accept responsibility for the water content of both the brain ventricles. Any disease that causes an increase in macromolecules in the ventricular fluid alters the osmotic gradient and causes hydrocephalus. Similarly, we can consider hydrocephalus to be a macromolecular clearance disorder. Evidence suggests that these macromolecules are cleared from the ventricles and brain into the venous system through the perivascular or lymphatic pathways.

Although there are also some gaps in this pathophysiological construct, it appears to have much more support.

9. Investigations

The International Guidelines have recommended the following key imaging features for the diagnosis of iNPH and the selection of patients shunt-responsive:

- Ventricular enlargement not entirely attributable to cerebral atrophy or congenital enlargement (Evans index > 0.3).
- Macroscopic obstruction to CSF flow.
- At least one of the following supportive features is available:
  - Enlargement of the temporal horns of the lateral ventricles is not entirely attributable to hippocampus atrophy.
  - Callosal angle of 40˚ or greater.
  - Evidence of altered brain water content, including changes in periventricular signal on CT and MRI, not attributable to microvascular ischemic changes or demyelination.
  - An aqueductal or fourth ventricular flow void on MRI.

The most commonly used radiological criteria in the diagnosis of hydrocephalus is given below:

- Ventriculomegaly (Evans' index > 0.3);
- Enlargement of the third ventricular recesses and lateral ventricular horns;
- Decreased mamillopontine distance and frontal horn angle;
- Thinning and elevation of the corpus callosum;
- Normal or narrowed cortical sulcus;
- Hyperintensities of the periventricular white matter (interstitial edema and acute hydrocephalus);
- The phenomenon of voids of the aqueductal flow in T2W images (a sign of communicating hydrocephalus).

10. CSF Removal

A high-volume spinal tap (>30 ml) (lumbar tap test) was the earliest method to establish the diagnosis of iNPH and predict the response to shunting and external lumbar drainage (ELD). A lumbar spinal catheter is inserted, and CSF is drained at a rate of 10 to 15 cm^3 per hour for 72 hours [45]. Although a commercially available automated gait analysis system can quantify response to ELD walking speed, it can also be measured using a timed 10-meter walk before and after ELD.

11. Comorbid Conditions

These deal with the comorbid conditions that occur during pregnancy; they are ruled out in the following:

11.1. Gestational Diabetes

It is the first major condition that causes hydrocephalus in infants, and its

incidence rate is high compared to the other causes that have been ruled out. The Journal of Biological Sciences reports that [46] maternal diabetes is associated with an increased risk of congenital abnormalities and growth deformities in the infant. Mothers with maternal diabetes may have a more permeable blood-brain barrier, which could increase CSF production of CSF and result in brain disorders such as hydrocephalus. According to Lawrence Jacob *et al.* [47], the interaction of the autonomic structures of the hypothalamic and brain stem by the increasing ventricles, even during the evolution of hydrocephalus, might indeed result in diabetes coexisting with normal pressure hydrocephalus.

11.2. Hypertension

Several more articles explain the causes of eclampsia or maternal pregnancy, which lead to subset impacts on hydrocephalus that arise in a congenital condition, and one of those articles is a review of the obstetric and perinatal outcomes in hypertension. This is the second significant comorbid condition that indirectly causes hydrocephalus. According to Sreelatha S. Kamala [48], there is a decrease in placental blood flow. An infant may get less oxygen and nutrients if the placenta does not get enough blood. Low birth weight, intrauterine growth restriction, and preterm birth can result from this. According to their case study, they observed that 2/3 of mothers had hypertension during pregnancy, which may be one reason why some children are born with congenital hydrocephalus. These led us to the conclusion that pregnant women with hypertension could even cause hydrocephalus [49].

11.3. Thyroid

It is another leading cause of hydrocephalus, which develops due to abnormal thyroid hormone levels during pregnancy. The newborn rat can be evaluated by comparing it with a human fetus in the second trimester of pregnancy and the newborn human baby with a 6-10-day-old rat, according to [50]. The hypothyroid brain exhibits numerous structural flaws; the cerebral cortex's cell density has increased due to decreased neuropil. Decreased cell counts in areas where postnatal cell acquisition is significant. Significantly reduced GABAergic interneuron density and increased neuronal precursor density in the cerebellum. Parvalbumin interneurons are less numerous in the cerebral cortex.

12. Conclusions

The clinical signs of hydrocephalus vary greatly from one person to another, depending on age, disease progression, and individual acceptance of the circumstance. Infants and young children, for instance, seem to be more vulnerable to symptoms of elevated intracranial pressure, such as vomiting, whereas adults may undergo loss of function, such as trying to walk or thinking. The capacity of an infant to compensate for increased CSF pressure and ventricle enlargement differentiates from an adult.

The complex interplay between comorbidities and environmental factors

highlights the multifactorial nature of hydrocephalus, particularly in pediatric cases. Maternal diabetes and hypertension during pregnancy have been identified as significant comorbidities that can increase the risk of hydrocephalus in children. Additionally, socioeconomic factors and exposure to environmental toxins or infections during pregnancy can also contribute to the development of hydrocephalus. Further research is needed to fully understand these intricate relationships and develop effective prevention and treatment strategies for hydrocephalus.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] LeDoux, J. (2023) The Deep History of Ourselves: The Four-Billion-Year Story of How We Got Conscious Brains. *Philosophical Psychology*, **36**, 704-715. https://doi.org/10.1080/09515089.2022.2160311

[2] Rao, D.B., Pardo, I.D., Chang, J.H., Bolon, B. and Garman, R.H. (2024) Nervous System. In: *Haschek and Rousseaux's Handbook of Toxicologic Pathology*, Elsevier, 633-738. https://doi.org/10.1016/b978-0-12-821046-8.00007-4

[3] Oliveira, L.B., Porto, S., Andreão, F.F., Ferreira, M.Y., Bocanegra-Becerra, J.E., Verly, G., *et al.* (2024) Are Ventriculopleural Shunts the Second Option for Treating Hydrocephalus? A Meta-Analysis of 543 Patients. *Clinical Neurology and Neurosurgery*, **244**, Article 108396. https://doi.org/10.1016/j.clineuro.2024.108396

[4] Agarwal, N. and Carare, R.O. (2021) Cerebral Vessels: An Overview of Anatomy, Physiology, and Role in the Drainage of Fluids and Solutes. *Frontiers in Neurology*, **11**, Article 611485. https://doi.org/10.3389/fneur.2020.611485

[5] Aschoff, A., Kremer, P., Hashemi, B. and Kunze, S. (1999) The Scientific History of Hydrocephalus and Its Treatment. *Neurosurgical Review*, **22**, 67-93. https://doi.org/10.1007/s101430050035

[6] Blitz, A.M., Ahmed, A.K. and Rigamonti, D. (2019) Founder of Modern Hydrocephalus Diagnosis and Therapy: Walter Dandy at the Johns Hopkins Hospital. *Journal of Neurosurgery*, **131**, 1046-1051. https://doi.org/10.3171/2018.4.jns172316

[7] Dandy, W.E. (1913) An Experimental and Clinical Study of Internal Hydrocephalus. *The Journal of the American Medical Association*, **61**, 2216-2217. https://doi.org/10.1001/jama.1913.04350260014006

[8] Shiota, K. (2008) Embryology of the Human Brain. *Donald School Journal of Ultrasound in Obstetrics and Gynecology*, **2**, 1-8. https://doi.org/10.5005/jp-journals-10009-1061

[9] William James, H., Boyd, J.D. and Mossman, H.W. (1945) Human Embryology (Prenatal Development of Form and Function).

[10] Winn, H.R. (2022) Youmans and Winn Neurological Surgery E-Book: 4-Volume Set. Elsevier Health Sciences.

[11] Bradley, W.G. (2014) CSF Flow in the Brain in the Context of Normal Pressure Hydrocephalus. *American Journal of Neuroradiology*, **36**, 831-838. https://doi.org/10.3174/ajnr.a4124

[12] Weed, L.H. (1914) Studies on Cerebro-Spinal Fluid. No. III: The Pathways of Escape from the Subarachnoid Spaces with Particular Reference to the ARACHNOID VILLI.

[13] Simon, M.J. and Iliff, J.J. (2016) Regulation of Cerebrospinal Fluid (CSF) Flow in Neurodegenerative, Neurovascular and Neuroinflammatory Disease. *Biochimica et Biophysica Acta* (*BBA*)—*Molecular Basis of Disease*, **1862**, 442-451. https://doi.org/10.1016/j.bbadis.2015.10.014

[14] Van Landingham, M., Nguyen, T.V., Roberts, A., Parent, A.D. and Zhang, J. (2009) Risk Factors of Congenital Hydrocephalus: A 10 Year Retrospective Study. *Journal of Neurology, Neurosurgery & Psychiatry*, **80**, 213-217. https://doi.org/10.1136/jnnp.2008.148932

[15] Kim, M., Park, S., Lee, J., Kim, H., Rhim, J.H., Park, S., *et al.* (2021) Differences in Brain Morphology between Hydrocephalus Ex Vacuo and Idiopathic Normal Pressure Hydrocephalus. *Psychiatry Investigation*, **18**, 628-635. https://doi.org/10.30773/pi.2020.0352

[16] Tullberg, M., Toma, A.K., Yamada, S., Laurell, K., Miyajima, M., Watkins, L.D., *et al.* (2024) Classification of Chronic Hydrocephalus in Adults: A Systematic Review and Analysis. *World Neurosurgery*, **183**, 113-122. https://doi.org/10.1016/j.wneu.2023.12.094

[17] Kahle, K.T., Klinge, P.M., Koschnitzky, J.E., Kulkarni, A.V., MacAulay, N., Robinson, S., *et al.* (2024) Paediatric Hydrocephalus. *Nature Reviews Disease Primers*, **10**, Article No. 35. https://doi.org/10.1038/s41572-024-00519-9

[18] Huang, J., Sarma, A., Little, S. and Pruthi, S. (2023) Systematic Approach to Pediatric Macrocephaly. *Radio Graphics*, **43**, e220159. https://doi.org/10.1148/rg.220159

[19] Sunderland, G., Ellenbogen, J. and Mallucci, C. (2023) Hydrocephalus. In: *Pediatric Surgery*, Springer, 499-525. https://doi.org/10.1007/978-3-030-81488-5_40

[20] Kirkpatrick, M., Engleman, H. and Minns, R.A. (1989) Symptoms and Signs of Progressive Hydrocephalus. *Archives of Disease in Childhood*, **64**, 124-128. https://doi.org/10.1136/adc.64.1.124

[21] Munch, T.N., Rasmussen, M.-H., Wohlfahrt, J., Juhler, M. and Melbye, M. (2014) Risk Factors for Congenital Hydrocephalus: A Nationwide, Register-Based, Cohort Study. *Journal of Neurology, Neurosurgery & Psychiatry*, **85**, 1253-1259. https://doi.org/10.1136/jnnp-2013-306941

[22] Abebe, M.S., Seyoum, G., Emamu, B. and Teshome, D. (2022) Congenital Hydrocephalus and Associated Risk Factors: An Institution-Based Case–Control Study, Dessie Town, North East Ethiopia. *Pediatric Health, Medicine and Therapeutics*, **13**, 175-182. https://doi.org/10.2147/phmt.s364447

[23] Walsh, S., Donnan, J., Morrissey, A., Sikora, L., Bowen, S., Collins, K., *et al.* (2017) A Systematic Review of the Risks Factors Associated with the Onset and Natural Progression of Hydrocephalus. *Neuro Toxicology*, **61**, 33-45. https://doi.org/10.1016/j.neuro.2016.03.012

[24] McAllister, J.P. (2012) Pathophysiology of Congenital and Neonatal Hydrocephalus. *Seminars in Fetal and Neonatal Medicine*, **17**, 285-294. https://doi.org/10.1016/j.siny.2012.06.004

[25] Del Bigio, M.R. (2001) Pathophysiologic Consequences of Hydrocephalus. *Neurosurgery Clinics of North America*, **12**, 639-649. https://doi.org/10.1016/s1042-3680(18)30022-6

[26] Bräutigam, K., Vakis, A. and Tsitsipanis, C. (2019) Pathogenesis of Idiopathic Normal Pressure Hydrocephalus: A Review of Knowledge. *Journal of Clinical Neuroscience*, **61**, 10-13. https://doi.org/10.1016/j.jocn.2018.10.147

[27] Orešković, D. and Klarica, M. (2010) The Formation of Cerebrospinal Fluid: Nearly

a Hundred Years of Interpretations and Misinterpretations. *Brain Research Reviews*, **64**, 241-262. https://doi.org/10.1016/j.brainresrev.2010.04.006

[28] Pickard, J. (1988) Physiology and Pathophysiology of the Cerebrospinal Fluid. *Journal of Neurology, Neurosurgery & Psychiatry*, **51**, 469-470. https://doi.org/10.1136/jnnp.51.3.469-a

[29] Soytürk, H., Yılmaz, M., Önal, C., Suveren, E. and Kılıç, Ü. (2022) Circulation of Cerebrospinal Fluid (CSF). In: *Cerebrospinal Fluid*, Intech Open, 21. https://doi.org/10.5772/intechopen.99621

[30] Xin, L., Madarasz, A., Ivan, D.C., Weber, F., Aleandri, S., Luciani, P., *et al.* (2024) Impairment of Spinal CSF Flow Precedes Immune Cell Infiltration in an Active EAE Model. *Journal of Neuroinflammation*, **21**, Article No. 272. https://doi.org/10.1186/s12974-024-03247-9

[31] Pudenz, R.H., Russell, F.E., Hurd, A.H. and Shelden, C.H. (1957) Ventriculo-Auriculostomy. A Technique for Shunting Cerebrospinal Fluid into the Right Auricle. *Journal of Neurosurgery*, **14**, 171-179. https://doi.org/10.3171/jns.1957.14.2.0171

[32] Avery, R.A., Shah, S.S., Licht, D.J., Seiden, J.A., Huh, J.W., Boswinkel, J., *et al.* (2010) Reference Range for Cerebrospinal Fluid Opening Pressure in Children. *New England Journal of Medicine*, **363**, 891-893. https://doi.org/10.1056/nejmc1004957

[33] Krishnamurthy, S. (2014) New Concepts in the Pathogenesis of Hydrocephalus. *Translational Pediatrics*, **3**, Article 185.

[34] Oresˇković, D., Whitton, P.S. and Lupret, V. (1991) Effect of Intracranial Pressure on Cerebrospinal Fluid Formation in Isolated Brain Ventricles. *Neuroscience*, **41**, 773-777. https://doi.org/10.1016/0306-4522(91)90367-w

[35] Orešković, D. and Klarica, M. (2011) Development of Hydrocephalus and Classical Hypothesis of Cerebrospinal Fluid Hydrodynamics: Facts and Illusions. *Progress in Neurobiology*, **94**, 238-258. https://doi.org/10.1016/j.pneurobio.2011.05.005

[36] Rasmussen, M.K., Mestre, H. and Nedergaard, M. (2022) Fluid Transport in the Brain. *Physiological Reviews*, **102**, 1025-1151. https://doi.org/10.1152/physrev.00031.2020

[37] Fujii, N., Nomura, S., Izuma, H. and Ishihara, H. (2024) Which Theory of Cerebrospinal Fluid Production and Absorption Do Neurosurgeons Teach to Medical Students? Survey from Medical Universities in Japan, 2022. *Neurologia Medico-Chirurgica*, **64**, 241-246. https://doi.org/10.2176/jns-nmc.2023-0277

[38] Warf, B.C. (2005) Comparison of 1-Year Outcomes for the Chhabra and Codman-Hakim Micro Precision Shunt Systems in Uganda: A Prospective Study in 195 Children. *Journal of Neurosurgery: Pediatrics*, **102**, 358-362. https://doi.org/10.3171/ped.2005.102.4.0358

[39] Harris, C., Khasawneh, A. and Garling, R. (2018) Cerebrospinal Fluid Circulation: What Do We Know and How Do We Know It? *Brain Circulation*, **4**, 14-18. https://doi.org/10.4103/bc.bc_3_18

[40] Frassanito, P., Goker, B. and Di Rocco, C. (2020) Aqueductal Stenosis and Hydrocephalus. In: *Textbook of Pediatric Neurosurgery*, Springer, 501-519. https://doi.org/10.1007/978-3-319-72168-2_20

[41] Klarica, M., Orešković, D., Božić, B., Vukić, M., Butković, V. and Bulat, M. (2009) New Experimental Model of Acute Aqueductal Blockage in Cats: Effects on Cerebrospinal Fluid Pressure and the Size of Brain Ventricles. *Neuroscience*, **158**, 1397-1405. https://doi.org/10.1016/j.neuroscience.2008.11.041

[42] Shapiro, K., Kohn, I.J., Takei, F. and Zee, C. (1987) Progressive Ventricular

Enlargement in Cats in the Absence of Transmantle Pressure Gradients. *Journal of Neurosurgery*, **67**, 88-92. https://doi.org/10.3171/jns.1987.67.1.0088

[43] Krishnamurthy, S., Li, J., Shen, Y., Duncan, T.M., Jenrow, K.A. and Haacke, E.M. (2018) Normal Macromolecular Clearance Out of the Ventricles Is Delayed in Hydrocephalus. *Brain Research*, **1678**, 337-355. https://doi.org/10.1016/j.brainres.2017.10.013

[44] Klebe, D., MBride, D., Krafft, P.R., Flores, J.J., Tang, J. and Zhang, J.H. (2019) Posthemorrhagic Hydrocephalus Development after Germinal Matrix Hemorrhage: Established Mechanisms and Proposed Pathways. *Journal of Neuroscience Research*, **98**, 105-120. https://doi.org/10.1002/jnr.24394

[45] Shooman, D., Portess, H. and Sparrow, O. (2009) A Review of the Current Treatment Methods for Posthaemorrhagic Hydrocephalus of Infants. *Cerebrospinal Fluid Research*, **6**, Article No. 1. https://doi.org/10.1186/1743-8454-6-1

[46] Jacobs, L. (1977) Diabetes Mellitus in Normal Pressure Hydrocephalus. *Journal of Neurology, Neurosurgery & Psychiatry*, **40**, 331-335. https://doi.org/10.1136/jnnp.40.4.331

[47] Ghorbani, Z.T. (2009) Maternal Diabetes Induced Hydrocephaly in Newborn Rats.

[48] Sreelatha, S.K. (2018) A Clinical Review of Obstetric and Perinatal Outcome in Thyroid Disorders. *Endocrinology & Metabolism International Journal*, **6**, 266-282. https://doi.org/10.15406/emij.2018.06.00188

[49] Gruber, R.W. and Roehrig, B. (2010) Prevention of Ventricular Catheter Obstruction and Slit Ventricle Syndrome by the Prophylactic Use of the Integra Antisiphon Device in Shunt Therapy for Pediatric Hypertensive Hydrocephalus: A 25-Year Follow-Up Study. *Journal of Neurosurgery*: *Pediatrics*, **5**, 4-16. https://doi.org/10.3171/2008.7.17690

[50] Noonan, J.A. and Ehmke, D.A. (1963) Complications of Ventriculovenous Shunts for Control of Hydrocephalus. *New England Journal of Medicine*, **269**, 70-74. https://doi.org/10.1056/nejm196307112690203