Hydrocephalus Pathophysiology

The **pathophysiology of hydrocephalus** refers to the mechanisms by which the abnormal accumulation of cerebrospinal fluid (CSF) leads to the characteristic features of the condition. Hydrocephalus is typically caused by a disruption in the production, circulation, or absorption of CSF, resulting in an increase in the volume of CSF within the ventricles of the brain. The condition can be classified as **obstructive (non-communicating)**, **communicating**, or **normal pressure hydrocephalus (NPH)**, each with distinct underlying pathophysiological mechanisms. Below is an overview of the key processes involved in the pathophysiology of hydrocephalus.

1. **Cerebrospinal Fluid (CSF) Dynamics** CSF is a clear fluid that cushions and nourishes the brain and spinal cord. It is produced by the choroid plexus in the ventricles, circulates through the ventricles, and is absorbed into the bloodstream via the **arachnoid villi** located in the subarachnoid space. The normal volume of CSF is about 150 ml, and it is continually produced and reabsorbed, maintaining a balance between production and absorption.

2. **Obstructive (Non-Communicating) Hydrocephalus** In **obstructive hydrocephalus**, the flow of CSF is blocked at some point along its pathway, causing an accumulation of CSF upstream of the obstruction. This leads to enlargement of the ventricles (ventriculomegaly) and increased intracranial pressure (ICP). The key features of this type of hydrocephalus include:

a. **Blockage of CSF Pathways** - The most common site of obstruction is the **aqueduct of Sylvius**, the narrow passage that connects the third and fourth ventricles. **Aqueductal stenosis**, often congenital, causes a blockage that prevents CSF from flowing freely from the third to the fourth ventricle, leading to the dilation of the lateral and third ventricles. - Other causes of obstruction include **brain tumors**, **cysts**, **vascular malformations**, or **inflammatory conditions** that physically block CSF flow. - The obstruction leads to the build-up of CSF in the ventricles, increasing their size and potentially causing damage to the surrounding brain tissue. Over time, the pressure can compress the brain and cause functional impairment.

b. **Ventricular Dilation** - As the CSF accumulates in the ventricles, the brain tissue may be compressed, leading to cortical thinning and damage to neuronal structures. - **Hydrocephalic brain**: Chronic, untreated hydrocephalus can result in “ventricular dilation” or an enlarged ventricle, which stretches and distorts the surrounding brain structures. This can result in cognitive and motor deficits due to damage to neural circuits.

3. **Communicating Hydrocephalus** In **communicating hydrocephalus**, there is no obstruction of CSF flow within the ventricles, but there is impaired absorption or reabsorption of CSF, leading to its accumulation. The key features of this type of hydrocephalus include:

a. **Impaired CSF Reabsorption** - The primary issue in communicating hydrocephalus is an inability of the **arachnoid villi** to adequately absorb CSF into the venous system. - This can be due to **inflammation**, **scarring**, or **obstruction** of the arachnoid villi, often caused by infections like **meningitis**, hemorrhages, or other traumatic injuries. - **Increased intracranial pressure** (ICP) occurs because the production of CSF continues at a normal rate, but it is not properly reabsorbed into the bloodstream, leading to a gradual increase in the volume of CSF in the ventricles.

b. **Normal Pressure Hydrocephalus (NPH)** - In **NPH**, there is an accumulation of CSF despite normal or near-normal intracranial pressure. The pathophysiology is thought to involve a gradual decrease in CSF absorption by the arachnoid villi, as well as an impaired ability of the brain to

accommodate the excess CSF volume. - This condition is often associated with **aging**, **brain atrophy**, or **prior trauma**. The key features of NPH are **gait disturbance**, **cognitive decline**, and **urinary incontinence**. - The exact mechanisms behind NPH remain unclear, but it is believed that the CSF accumulation leads to **ventricular enlargement**, which distorts brain structures and interferes with the normal functioning of the **cortex**, particularly in areas responsible for motor control, cognition, and bladder function.

4. **Hydrocephalus Ex-Vacuo** Hydrocephalus ex-vacuo occurs when there is a loss of brain tissue due to injury or disease, and the remaining tissue is displaced, causing an increase in the size of the ventricles. This condition is typically seen in neurodegenerative disorders such as **Alzheimer's disease**, **stroke**, or **brain injury**. In these conditions, brain atrophy leads to enlarged ventricles that are filled with CSF, though there is no actual obstruction or impaired CSF circulation.

5. **Pathophysiological Mechanisms Involving Increased Intracranial Pressure (ICP)** In all forms of hydrocephalus, the increased volume of CSF leads to elevated intracranial pressure (ICP), which can have significant effects on brain function. Elevated ICP can lead to:

- **Brain compression**: Increased pressure can compress brain tissue, reducing blood flow and leading to **hypoxia** (lack of oxygen) and **ischemia** (restricted blood flow), which damages neurons and glial cells. - **Cerebral edema**: Swelling of the brain tissue, further increasing ICP and exacerbating the damage. - **Displacement of brain structures**: Severe cases of hydrocephalus can cause herniation of brain structures through openings in the skull, such as the foramen magnum, which can be life-threatening.

6. **Neuroplasticity and Compensation** In some cases, especially in children or individuals with slow-progressing hydrocephalus, the brain may attempt to compensate for the increased volume of CSF. This can involve:

- **Expansion of the subarachnoid space**: This allows the brain to accommodate the increased CSF volume without significant cortical damage in the early stages. - **Neuroplasticity**: The brain may reorganize itself, forming new neural connections to compensate for the loss of function in affected areas.

However, this compensatory ability has its limits, and prolonged or severe hydrocephalus can lead to irreversible brain damage.

7. **Molecular Mechanisms and Cellular Changes** Recent research in the pathophysiology of hydrocephalus has focused on the molecular and cellular changes that occur in response to CSF accumulation. These changes include:

- **Astrocyte activation**: Astrocytes, the star-shaped glial cells in the brain, may become activated in response to pressure changes, leading to **gliosis** (a form of scar tissue formation). - **Cytokine release**: Inflammatory mediators like cytokines are often released in response to the increased pressure and mechanical stress on brain tissue, which can lead to further neuronal injury. - **Blood-brain barrier disruption**: The increased ICP can compromise the integrity of the blood-brain barrier, making the brain more susceptible to injury from toxins and infections.

Conclusion: The pathophysiology of hydrocephalus involves complex interactions between abnormal CSF production, flow, and absorption, leading to increased intracranial pressure and subsequent damage to brain tissue. Different forms of hydrocephalus, including obstructive, communicating, and normal pressure hydrocephalus, have distinct underlying mechanisms, but all share the common feature of CSF accumulation. Understanding the pathophysiology of hydrocephalus

is crucial for developing effective treatments and interventions aimed at reducing brain damage and improving patient outcomes.

Aquaporin 4 channels are implicated in the pathophysiology of hydrocephalus, a disease of water imbalance that leads to CSF accumulation in the ventricular system. Many molecular aspects of fluid exchange during hydrocephalus have yet to be firmly elucidated, but a review of the literature suggests that modulation of AQP4 channel activity is a potentially attractive future pharmaceutical therapy. Drug therapy targeting aquaporin channels may enable control over water exchange to remove excess CSF through a molecular intervention instead of by mechanical shunting [1].

History

Research into the pathophysiology of hydrocephalus began with the work of Dandy and Blackfan in the early decades of the twentieth century [2].

At that time little was known about the pathophysiology of hydrocephalus. Plain radiography and lumbar puncture were the only studies that could be performed on hydrocephalic patients or experimental animals. Late in his career, Dandy was influential in the development of pneumoventriculography, which first allowed neuroanatomic features to be defined in living patients and animal models.

Initially, these investigators were limited to studying hydrocephalus using ventricular puncture and lumbar puncture. With these tools, Dandy and his pediatrician colleague, Blackfan, performed ventricular punctures and injected supravital dyes into ventricles and later performed lumbar punctures. If the dye was recovered in the spinal tap, the hydrocephalus was classified as “communicating.” If no dye was recovered in the lumbar theca, the hydrocephalus was considered “obstructive” or “non-communicating.” Dandy also performed experiments that defined the choroid plexus as the source of the production of CSF [3] [4].

Based on these experiments and on clinical observations, Dandy and later investigators developed techniques designed to treat or at least to ameliorate hydrocephalus, which at that time was essentially a death sentence. Dandy and others attempted to perform internal bypasses called third ventriculostomies via an open craniotomy or endoscopically via a cystoscope or choroid plexectomy. In general, all of these techniques were unsuccessful due to the severity of the hydrocephalus diagnosed in those times.

This classification of communicating or obstructive (non-communicating) was extremely useful for understanding hydrocephalus as well as for guiding the search for therapeutic options for the management of the condition. Soon, however, the classification was recognized as an inadequate portrayal of the pathophysiology underlying hydrocephalus. In a brilliant but infrequently cited study, Ransohoff and colleagues reviewed and updated Dandy's ideas. [5]. These researchers realized that the crude techniques available to Dandy were inadequate to understand the spectrum of diseases that led to hydrocephalus. They updated the classification to incorporate what was then understood of the pathophysiology of the condition and proposed that Dandy's classification be modified.

Ransohoff et al postulated that there were a variety of potential sites of obstruction to the flow of CSF and thought that all hydrocephalus was obstructive [6]. Using the same criteria that Dandy had used, Ransohoff's group agreed that patients had obstructive hydrocephalus when dye in the ventricles did

not communicate with the lumbar theca. However, they believed that the point of obstruction was at the aqueduct of Sylvius or at the outlet foramina of the fourth ventricle. They suggested that this form of hydrocephalus be called “intraventricular obstructive” hydrocephalus. They still believed that hydrocephalus associated with CSF flow from the ventricular system to the lumbar theca was an obstructive process involving scarring of the cortical subarachnoid spaces or failure of the terminal absorption of CSF, presumably, by the arachnoid villi. They proposed that this condition should be called “extraventricular obstructive” hydrocephalus [7].

This nomenclature was useful for a variety of reasons. At that time the only available form of treatment for intraventricular obstructive hydrocephalus involved shunting from the ventricle to the atrium of the heart, ureter, or occasionally to the peritoneum. If the lumbar theca was found to be in communication with the ventricular system, the somewhat safer option of shunting the lumbar theca was possible. At this point, effective surgical treatments became available for the control of hydrocephalus, and the Ransohoff classification was useful in selecting from the several treatment paradigms.

In 1973 the first computerized tomography (CT) scanner was installed in the United States. For the first time, noninvasive techniques were available to define the point of obstruction in hydrocephalus. In the early 1980s magnetic resonance imaging (MRI) became available and provided improved resolution to define the actual point of obstruction of CSF flow that led to hydrocephalus. Hydrocephalus progressed from two types, as defined by the techniques available to Dandy, to multiple finite types that could be defined and treated by specific techniques [8].

1)
Desai B, Hsu Y, Schneller B, Hobbs JG, Mehta AI, Linninger A. Hydrocephalus: the role of cerebral aquaporin-4 channels and computational modeling considerations of cerebrospinal fluid. Neurosurg Focus. 2016 Sep;41(3):E8. doi: 10.3171/2016.7.FOCUS16191. PubMed PMID: 27581320.
2) , 3)
Dandy W. Internal hydrocephalus, an experimental, pathological and clinical study. Am J Dis Child. 1914;8:406–482.
4)
Dandy W. Experimental hydrocephalus. Ann Sug. 1919;70:129–142.
5) , 6) , 7)
RANSOHOFF J, SHULMAN K, FISHMAN RA. Hydrocephalus: a review of etiology and treatment. J Pediatr. 1960 Mar;56:399-411. PubMed PMID: 14436205.
8)
Rekate HL. The definition and classification of hydrocephalus: a personal recommendation to stimulate debate. Cerebrospinal Fluid Res. 2008 Jan 22;5:2. doi: 10.1186/1743-8454-5-2. PubMed PMID: 18211712; PubMed Central PMCID: PMC2263019.