جامعة الملك سعود
King Saud University
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07

Pathology

(Congenital Malformation and hydrocephalus)

439

Color index

- Important
- Doctor's note
- Extra info
- Main text

"اللهم لا سهل الا ماجعلته سهلا و انت تجعل الحزن إذا شئت سهلا"

Objective

01 Know the common types of congenital malformations of the CNS and have a basic knowledge of their pathological features

02 Correlate CNS normal development with the classification of congenital CNS malformations

03 Appreciate the role of folate deficiency as an etiological factor in neural tube defects and understand the role of Alpha fetoprotein measurement and ultrasound in antenatal diagnosis of neural tube defects

04 Understand the various mechanisms that lead to the development of hydrocephalus

05 List and classify the main causes of hydrocephalus

Overview

PART I — Congenital Malformation

- **Neural Tube Defects**
  - Spina Bifida Occulta
  - Myelomeningocele
  - Anencephaly
  - Encephalocele
- **Forebrain Malformations**
  - Megalencephaly
  - Microencephaly
  - Lissencephaly
- **Posterior Fossa Anomalies**
  - Type 1 Chiari malformation
  - Type 2 Chiari malformation (Arnold Chiari malformation)

PART II — Hydrocephalus

- **Causes**
  - Hypersecretion of CSF
  - Defective filtration of CSF
  - Obstructive hydrocephalus
- **Types**
  - Communicating Hydrocephalus
  - Noncommunicating Hydrocephalus

Congenital Malformations

- The incidence of CNS malformations, giving rise to Mental retardation, cerebral palsy (clinical term used describing loss of brain function) or neural tube defect is estimated at 1% to 2%
- Malformations of the brain are more common in the setting of multiple birth defects.
- Because different parts of the brain develop at different times during gestation (and afterwards), the timing of an injury will be reflected in the pattern of malformation. *injury in the first stages of pregnancy will lead to more severe lesions
- Prenatal or perinatal insults may either cause:
  - **Failure of normal CNS development.** (giving rise to mental retardation, cerebral palsy or neural tube defects)
  - **Tissue destruction.**
- Most cases of congenital malformations will be apparent on prenatal screening tests and ultrasounds. However, if prenatal care was limited, these congenital defects are usually readily visible at the time of birth. In some mild cases, for example, **spina bifida occulta**, diagnosis may not occur until adulthood.

Etiology & pathogenesis :

The pathogenesis and etiology of many malformations remain unknown. However, it has multiple factors.

Genetic factors:

Mutations affecting genes that regulate the differentiation, maturation, development or intercellular communication (connections) of neurons or glial cells

Environmental Factors:

Toxic compounds, infectious agents, various chemicals

Neural Tube Defect

Introduction :

- Neural tube defects are the **most frequent CNS malformations**
- Failure of a portion of the neural tube to close, or reopening after successful closure may lead to one of several malformations.
- All these malformations are characterized by abnormalities involving some combination of neural tissue, meninges, overlying bone or soft tissues or skin.
- The most common defects involve the posterior end of the neural tube, from which the spinal cord forms.

Risk factors :

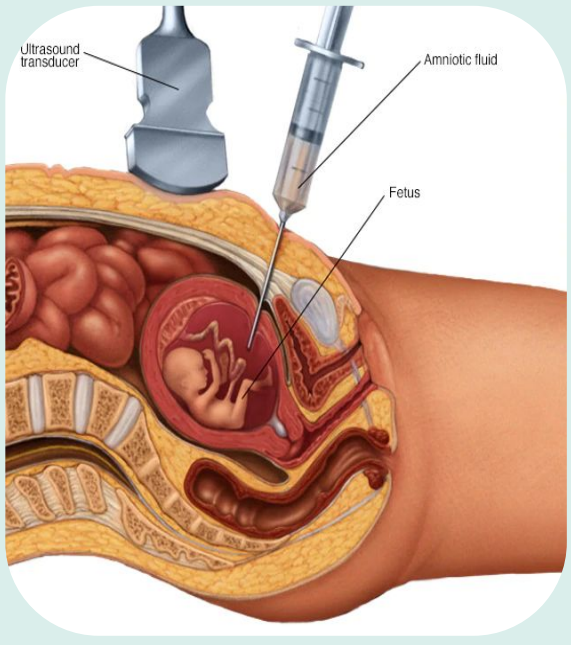
The overall recurrence risk in subsequent pregnancies is 4% to 5%.

★ **Folate deficiency** during the initial weeks of gestation

- Prenatal vitamins are aimed as administration of folate to women of child-bearing age reduces the incidence of neural tube defects by up to 70%

★ **Elevated α-fetoprotein** in serum and/or **amniotic fluid**

- High levels of α-fetoprotein may suggest that the developing baby has a neural tube defect such as: **meningocele**, **myelomeningocele** or **anencephaly**, **but <u>not</u> spina bifida occulta**.

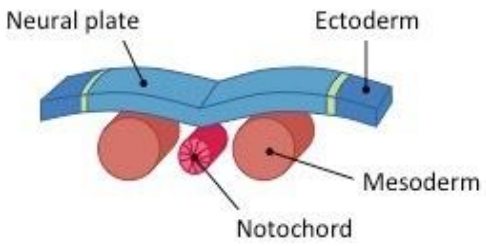


- The combination of ultrasound and maternal screening for elevated α-fetoprotein has **increased early detection** of neural tube defects.

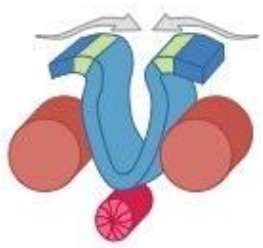
Neural Tube Defect

Brief Embryology Revision !

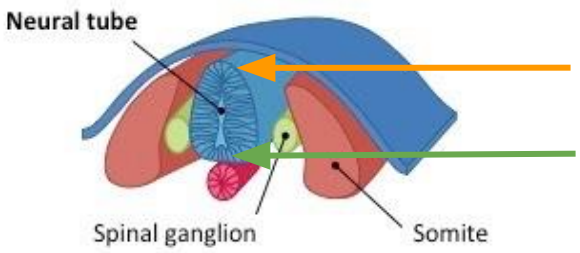
Notochord explanation was only found in girl's slides



1. Notochord forms from mesoderm cells soon after gastrulation is complete



2. Signals from notochord cause inward folding of ectoderm at the neural plate



3. Ends of neural plate fuse and disconnect to form an autonomous neural tube

Anterior (cranial) end: develops into brain

Posterior (caudal) end: develops into spinal cord

- Among the earliest stages in brain development is the formation of the neural tube.
- The inside lumen of the neural tube (neural canal), will form both the ventricular system of the brain and the central canal of the spinal cord.

Overview of Diseases

- **Neural Tube Defects**
  - **Affecting brain**
    *Results as a failure of closure of the anterior end of neural tube
    - **Anencephaly**
    - **Encephalocele**
  - **Affecting spinal cord**
    *Results as a failure of closure of the posterior end of neural tube
    - **Spina bifida occulta**
    - **Spina bifida cystica**
      - **Myelomeningocele**
      - **Meningocele**

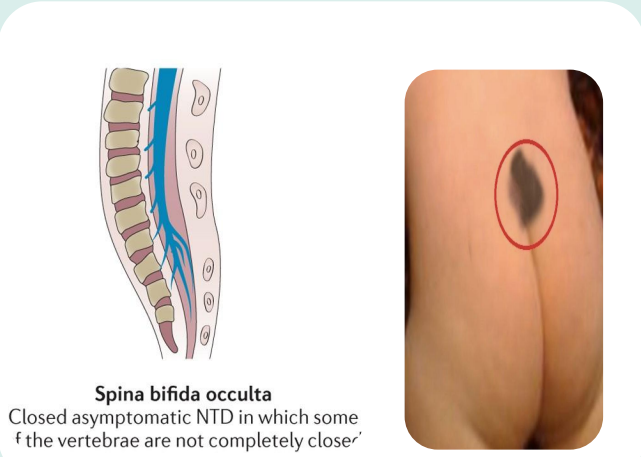
Video

Neural Tube Defects

01 Spina bifida occulta

← only found in girl's slides

- **Asymptomatic** bony defect
- Caused by failure of fusion of the halves of vertebral arches.
- Skin overlying is intact but might show a depression (dimpling) due to failure of fusion of vertebral arches, sometimes covered by a tuft of hair.

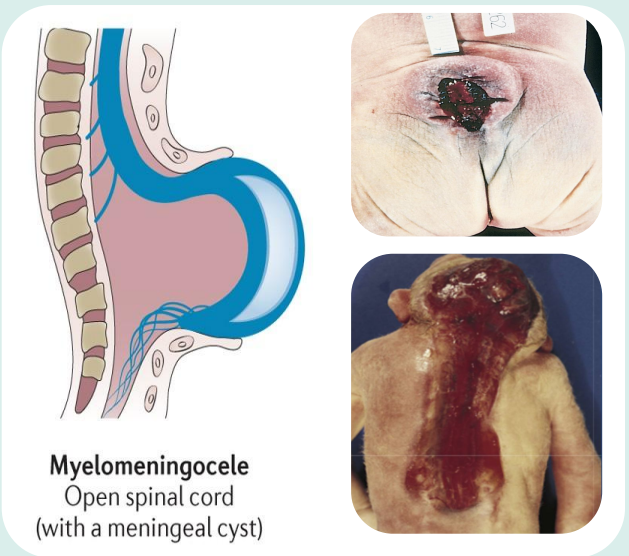


Spina bifida occulta
Closed asymptomatic NTD in which some of the vertebrae are not completely closed

02 ★★Myelomeningocele (Spina bifida cystica)

*Myelo= spinal cord
*meningo= meninges
*cele = hernia (فتق)

- Severe malformation consisting of a flat, disorganized segment of spinal cord associated with an overlying meningeal outpouching (extension of CNS tissue) through a defect in the vertebral column
- it is due to failure of vertebral arches to close with herniation of both meninges and spinal cord
- Most commonly occur in the lumbosacral region.



Myelomeningocele
Open spinal cord (with a meningeal cyst)

*Meningomyelocele occupying the whole neural tube. (very rare)

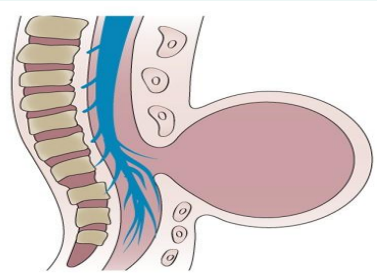
Symptoms

- **Motor** and **sensory** deficits in the **lower** extremities.
- Problems with **bowel** and **bladder control**. *defects in the micturition process
- The symptoms derive from the abnormal spinal cord in this region, and are often compounded by infections extending from thin or ulcerated overlying **skin**. *infections are due to exposure of the spinal cord to the air attracting microbes
- Associated with type II Arnold-Chiari syndrome

EXTRA

Meningocele (Spina bifida cystica)

- Outpouching of skin, meninges, Cerebrospinal fluid without bulging of neural tissue like Myelomeningocele

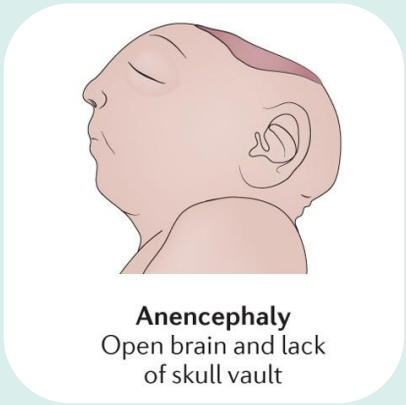


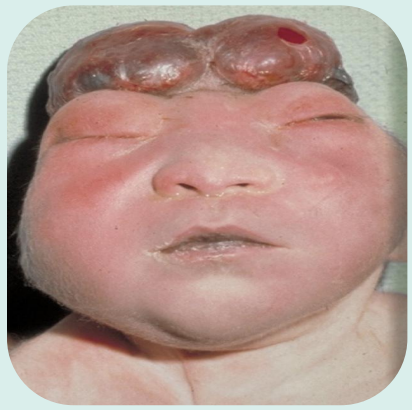
Meningocele
Protrusion of the meninges (filled with CSF) through a defect in the skull or spine

Neural Tube Defects

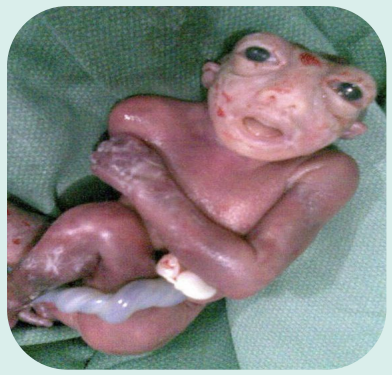
03 Anencephaly

- Anencephaly is a malformation of the anterior end of the neural tube, with absence of the brain and top of skull.





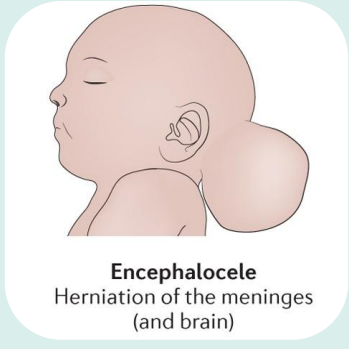
- Children born with anencephaly die shortly after birth.



04 Encephalocele

- Also known as cranium bifidum
- Describes a rare defect where a baby's skull does not close properly during development leading to a diverticulum (outpouching) of malformed CNS tissue extending through the defect in the cranium.
- The portion of the brain that sticks outside the skull is usually covered by skin or a thin membrane so that the defect resembles a small sac
- It most often involves the occipital region, the posterior fossa, ear or nose
- Affected individuals may have normal intelligence, while others experience intellectual disability, depending upon many different factors including size, location and the amount and kind of brain tissue protruding from the skull

*To read more about Encephalocele **click here!**



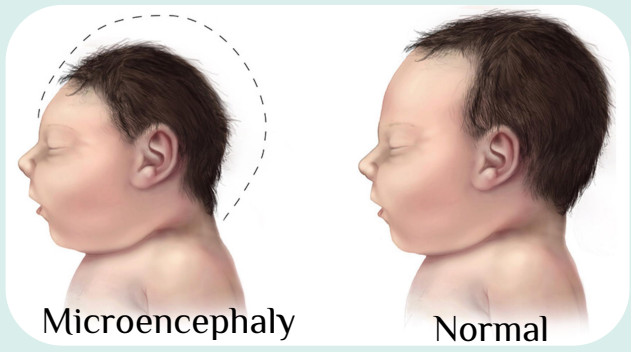
Forebrain Malformations

01 Megalencephaly

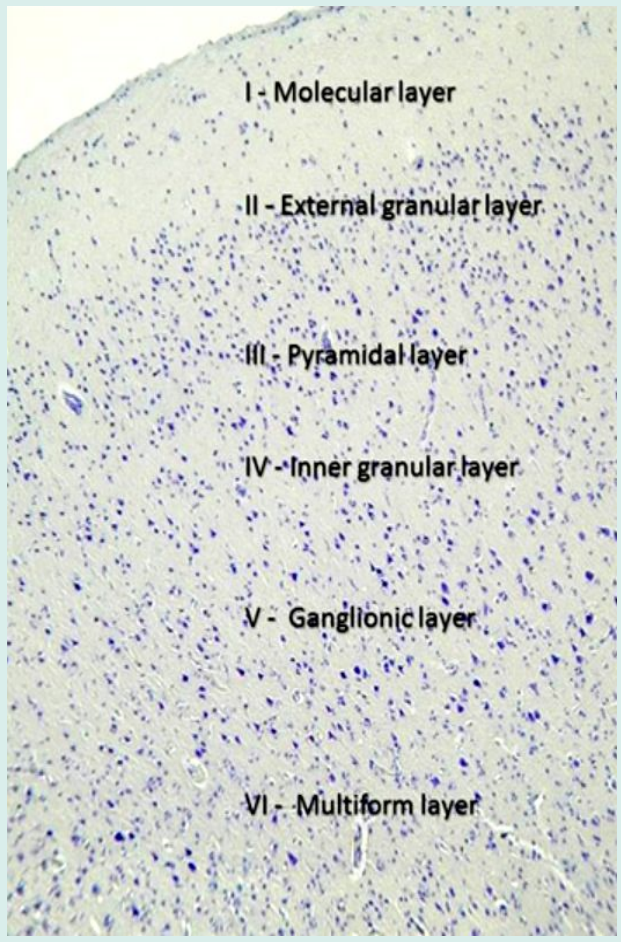
*Encephal : Brain
*Cephal : Head

- Rare genetic disorders.
- The volume of brain is abnormally **large**.

02 Microencephaly



- More common
- It describes a group of malformations in which the volume of brain is too small
- Usually associated with a small **head**, Microcephaly
- **Occurs in a wide range of clinical settings, including:**
  1. Chromosome abnormalities
  2. Fetal alcohol syndrome
  3. Human immunodeficiency virus type-1 (HIV-1) and Zika virus infection acquired in utero



Six-layered neocortical architecture

- The unifying feature of all causes is associated with a **decreased number of neurons destined for the cerebral cortex**
- Disruption of normal neuronal migration from the ventricles to the cortex and differentiation during development can lead to a **disruption of the normal gyration and six-layered neocortical architecture**
- The normal cortex consists of 6 layers. The cells of these layers originate around ventricles then travel to the cortex (called **migration**) .

Robbins: During the early stages of brain development, as progenitor cells proliferate in the subependymal ventricular zone, the balance between cells leaving the progenitor population to form the cortex and those remaining in the proliferating pool affects the overall number of neurons and glial cells generated. If too many cells leave the progenitor pool prematurely, there is inadequate generation of mature neurons, leading to a small brain

Forebrain Malformations

03 Lissencephaly (Agyria)

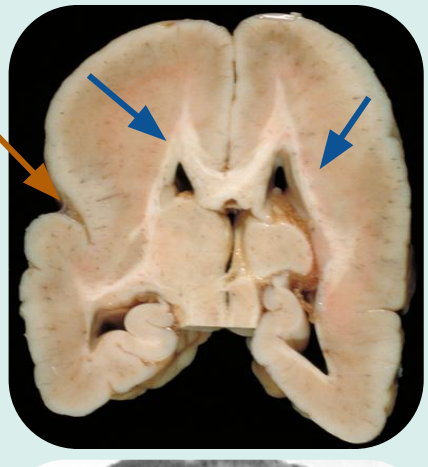
- Characterized by an absence of normal gyration and a smooth-surfaced brain due to failure of neuronal cell migration
- **Pachygyria** is a more patchy involvement by an absence of normal gyration
- Lissencephaly: diffuse loss of gyri → agyria
- Pachygyria: patchy loss of gyri
- The condition is characterized by agyria or pachygyria, which means absence or incomplete development, respectively, of the brain gyri or convolution, causing the brain's surface to appear unusually smooth
- Lissencephaly (meaning "smooth brain") is a set of rare brain disorders where the whole or parts of the surface of the brain appear smooth. It is caused by defective neuronal migration during the 12th to 24th weeks of gestation resulting in a lack of development of brain folds (gyri) and grooves (sulci).

Characteristics

- Single-gene defects have been identified in some cases of lissencephaly.
- The cortex is abnormally thickened and is usually only four-layered.

Gross features

- Cortical sulci are absent **except for the** Sylvian fissure.
- The cortex is **thick** and consists of the molecular and three other neuronal layers (four in total which is abnormal)
- The deepest of these layers is also the thickest and most cellular, presumably comprised of neurons that migrated a certain distance from the ventricles but **failed to reach their normal destinations.**
- There is a small amount of myelinated white matter between the abnormal cortex and the ventricles.



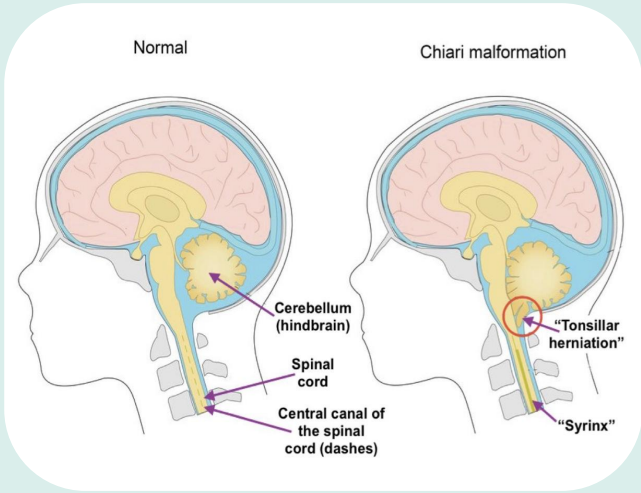
*To read more about Lissencephaly **click here!**

Posterior Fossa Anomalies

- The most common malformations in posterior fossa result in either **misplaced** or **absent cerebellum**.

- The posterior fossa is a narrow region so typically, any abnormality of this region is associated with neural tube defects and **hydrocephalus** *will be discussed later in the lecture

- Anomalies:
  - Type 1 Chiari malformation
  - Type 2 Chiari malformation
  - Type 3 Chiari malformation



What is Chiari's Malformation? It's the caudal displacement of the cerebellum with/without the medulla oblongata, through the foramen magnum.

	Type 1 Chiari malformation only found in girl's slides	Type 2 ★★ Chiari malformation (Arnold-Chiari malformation)
Definition	(Mild/ less severe) Low-lying extension of **cerebellar tonsils** through the foramen magnum at the base of the skull.	(Severe) ★ Downward extension of **vermis**, cerebellar tonsils and medulla oblongata into the foramen magnum causing hydrocephalus
Features	- Obstruction of CSF flow and compression of the medulla due to the extension - Results in symptoms of **headache** or **cranial nerve deficits**. - Increasing the space or the tissue in the posterior fossa through neurosurgery can alleviate the symptoms	- Small posterior fossa - Misshapen midline cerebellum - Some cranial nerves are pressed and extended into the foramen magnum Closely associated with the presence of : - Hydrocephalus - Lumbar myelomeningocele

"The following part has no connection to the previous part, they are two different topics in one lecture"

Cerebrospinal fluid (CSF)

1. CSF is produced by the choroid plexus within the ventricles
2. It circulates through the ventricular system and exits through the Foramina of Luschka and Magendie
3. CSF then fills the subarachnoid space around the brain and spinal cord

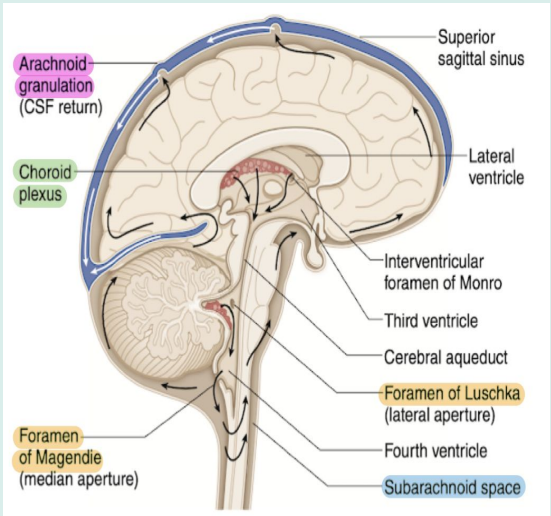


Figure III-3-2. Sagittal Section of the Brain

interventricular foramen of Monro cerebral aqueduct
Lateral ventricles → third ventricle → fourth ventricle → subarachnoid space
(via foramina of Luschka and foramen of Magendie)

4. It contribute to the cushioning of the nervous system within its bony confines
5. The arachnoid granulations are responsible for the resorption of CSF
6. The balance between CSF generation and resorption keeps the volume of this fluid stable

Hydrocephalus

- Hydrocephalus refers to the accumulation of excessive CSF within the ventricular system which in turn may lead to an increased intracranial pressure (ICP) and ventricular dilation.
- **Most cases** occur as a consequence of impaired flow or impaired reabsorption of CSF (most likely as a result of an obstructive cause, check next slide!)
- In **rare instances** overproduction of CSF may be responsible (e.g. tumors of the choroid plexus)
- It is <u>not</u> considered as a congenital malformation but it can be associated with it . It is a sign (a sign is what the doctor discovers, a symptom is what the patient tells)

Hydrocephalus in infancy:

Hydrocephalus in infant before closure of sutures → Results in enlargement of the head

Hydrocephalus in infant after fusion of sutures → Results in expansion of the ventricles and increased intracranial pressure, without a change in head circumference. It is dangerous because it can lead to hernia of the brain → death

**The spaces between bones (cranial sutures) remain open in babies and young children for about 12 to 18 months.

Hydrocephalus

Causes

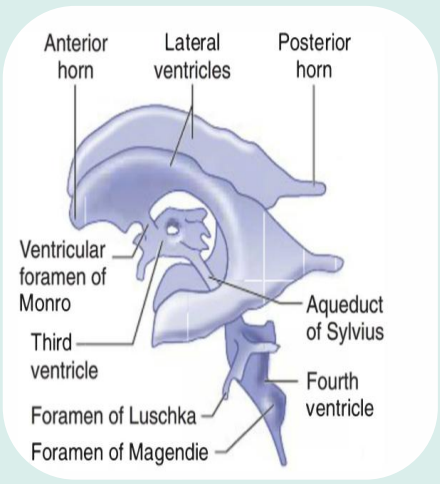
01 **Hypersecretion of CSF,** e.g. choroid plexus tumor *papilloma (rare)

03 **Defective filtration of CSF,** Postulated for low-pressure hydrocephalus. Very rare and not fully understood .

02 **Obstructive hydrocephalus: ★★**

- ❖ **Foramina of Monro** obstruction e.g. colloid cyst.
- ❖ **Third ventricle** obstruction e.g. pilocytic astrocytoma.
- ❖ **Aqueduct** obstruction e.g. aqueductal stenosis or atresia and posterior fossa tumors.
- ❖ Foramina of **Luschka** obstruction **or impairment of flow from the fourth ventricle** (Chiari malformation, meningitis, subarachnoid hemorrhage, posterior fossa tumors).
- ❖ Fibrosis of the **subarachnoid space** e.g. meningitis, subarachnoid hemorrhage,meningeal dissemination of tumors.

Dr.hisham : memorize each region with its example!!



Explanation: A tumor around a ventricle can lead to → obstruction → lack of circulation of CSF → accumulation of the fluid → dilatation of the ventricle (localized not generalized hydrocephalus)

Types:

	Noncommunicating Hydrocephalus **Cause of naming:** no communication between subarachnoid space and ventricles	Communicating Hydrocephalus **Cause of naming:** There is communication between subarachnoid space and ventricles
Cause	- Obstacle to the flow of CSF within the ventricular system (local accumulation of the fluid) - CSF production is normal	Can arise from 3 causes: - **Reduced CSF absorption** - CSF hypersecretion - CSF Defective filtration (circulation blockage)
Manifestation	- A portion of the ventricles enlarges while the remainder does not - Most commonly seen with masses at the foramen of Monro, aqueduct of Sylvius, cysts or tumor	All of the ventricular system is enlarged

Take home massage

- Malformations of the brain can occur because of genetic factors or external insults.
- The timing of the injury will determine the pattern of the injury, based on the type of developmental processes occurring at the point of injury.
- Patterns of malformation include alterations in the closure of the neural tube, proper formation of the separate portions of the neural tissue, and migration of neurons to the appropriate locations.
- Hydrocephalus is an increase in CSF volume within all or part of the ventricular system.

Homework

1- Define: meningocele:

Protrusion of the membranes of the brain or SC through a defect in the cranium or spinal column.

2- Define: polymicrogyria:

Characterized by increased number of irregularly formed gyri that result in a bumpy surface.

3- What is the difference between microcephaly and microencephaly?

Microcephaly: Small head (skull). Microencephaly: Small brain.

4- Define: hydrocephalus ex vacuo:

A compensatory increase in CSF volume may occur secondary to a loss of brain volume from any underlying cause (e.g., infarction, neurodegenerative disease).

QUIZ!

MCQs

01 | which one of the following malformation caused by failure of fusion of the halves of vertebral arches?			
A) spina bifida occulta	B) myelomening-ocele	C) anencephaly	D) encephalocele
02 | which one of the following is malformation of the anterior end of the neural tube?			
A) spina bifida occulta	B) myelomening-ocele	C) anencephaly	D) encephalocele
03 | which one of the following malformation is most common in lumbosacral region?			
A) spina bifida occulta	B) myelomening-ocele	C) anencephaly	D) encephalocele
04 | which one of the following Forebrain malformation is usually associated with a small head?			
A) Megalencephaly	B) Microcephaly	C) Pachygyria	D) Microencephaly
05 | A 5-month-old male patient, presented to A&E department following parental concerns about abnormal movements and developmental regression, MRI shows absence of normal gyration and a smooth-surfaced brain. What also you do expect to see?			
A) the cortex is thick and consists of three layers	B) the cortex is thick and consists of four neuronal layers	C) unmyelinated white matter between the abnormal cortex and the ventricles	D) Cortical sulci are absent in the whole of brain
06 | Which one of the following is an obstructive cause of the third ventricle can lead to Hydrocephalus ?			
A) choroid plexus tumor	B) Colloid cyst	C) pilocytic astrocytoma	D) subarachnoid hemorrhage

MCQs Answer key	01	02	03	04	05	06
	A	C	B	D	B	C

Summary

Congenital Malformation	
Etiology	Etiology of many malformations remain unknown, both genetic and environmental factors are clearly at play: Mutation, toxic compounds, infectious agents
Some examples of congenital malformation:	**1. Neural tube defect:** Failure of a portion of the neural tube to close, or reopening after successful closure may lead to one of several malformations. Characterized by abnormalities involving some combination of neural tissue, meninges, overlying bone or soft tissues **Risk factors:** Folate deficiency during the initial weeks of gestation **Types:** Myelomeningocele (Extension of CNS tissue through a defect in the vertebral column) Anencephaly (malformation of the anterior end of the neural tube + absence of the brain and top of skull) Encephalocele (diverticulum of malformed CNS tissue extending through a defect in the cranium) **2. Forbrain malformation: Types:** Megalencephaly (volume of brain abnormally large) Microencephaly (volume of brain abnormally small) (more common) Lissencephaly (absence of normal gyration and a smooth-surfaced brain) **Causes :** Chromosome abnormalities, Fetal alcohol syndrome, Human immunodeficiency virus 1 (HIV-1) 3. **Posterior Fossa Anomalies:** The most common malformations in this region of the brain result in either misplaced or absent cerebellum. **Types:** Arnold-Chiari malformation type 1 & 2

Hydrocephalus	
Definition	Hydrocephalus refers to the accumulation of excessive CSF within the ventricular system
Causes	Impaired flow or impaired resorption of CSF, in very rare instance overproduction of CSF may be responsible
Types	- Communicating hydrocephalus: all of the ventricular system is enlarged - Non-communicating hydrocephalus: a portion of the ventricles enlarges while the remainder does not

"اللهم علمنا ماينفعنا ، وانفعنا بما علمتنا وزدنا علما يارب العالمين"

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Special thanks to **Sarah AlAidarous, Sarah Alobaid** for their effort !

Any future corrections will be in the editing file , Click

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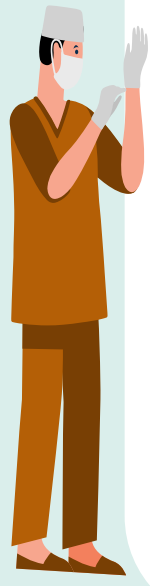

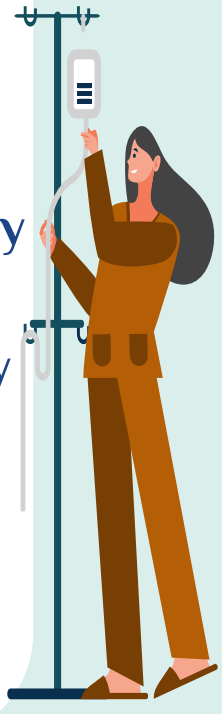

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