Lecture 8
Congenital Malformations & Hydrocephalus

PATHOLOGY TEAM 435

{ ومن لم يذق مرّ التعلُّمِ ساعةً.. تجرع ذلَّ الجهل طوال حياتهِ }

Revised by

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Red: Important. Grey: Extra Notes Doctors Notes will be in text boxes

Objectives:

- Know the common types of congenital malformations of the CNS and have a basic knowledge of their pathological features.
- Correlate CNS normal development with the classification of congenital CNS malformations.
- 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.
- Understand the various mechanisms that lead to the development of hydrocephalus.
- List and classify the main causes of hydrocephalus.

Background:

The incidence of CNS malformations, giving rise to mental retardation, cerebral palsy, or neural tube defects, is estimated at 1% to 2%. Malformations of the brain are more common in the setting of multiple birth defects. Prenatal or perinatal insults may either cause failure of normal CNS development or result in tissue destruction.

Hydrocephalus is abnormal buildup of cerebrospinal fluid (CSF) in the ventricles of the brain. It can result from congenital and acquired etiologies. The fluid is often under increased pressure (but not always) and can compress and damage the brain.

Key principles to be discussed:

- CNS congenital malformation incidence and introduction to the basic concepts behind the pathogenesis. These include genetic and environmental factors and the role of the stage of gestation development.
- Definition and pathological changes in forebrain anomalies:
  - Megalencephaly, microencephaly and lissencephaly.
- Microencephaly causes.
- Definition and pathological changes in neural tube defects:
  - Meningomyelocele, spina bifida, anencephaly and encephalocele.

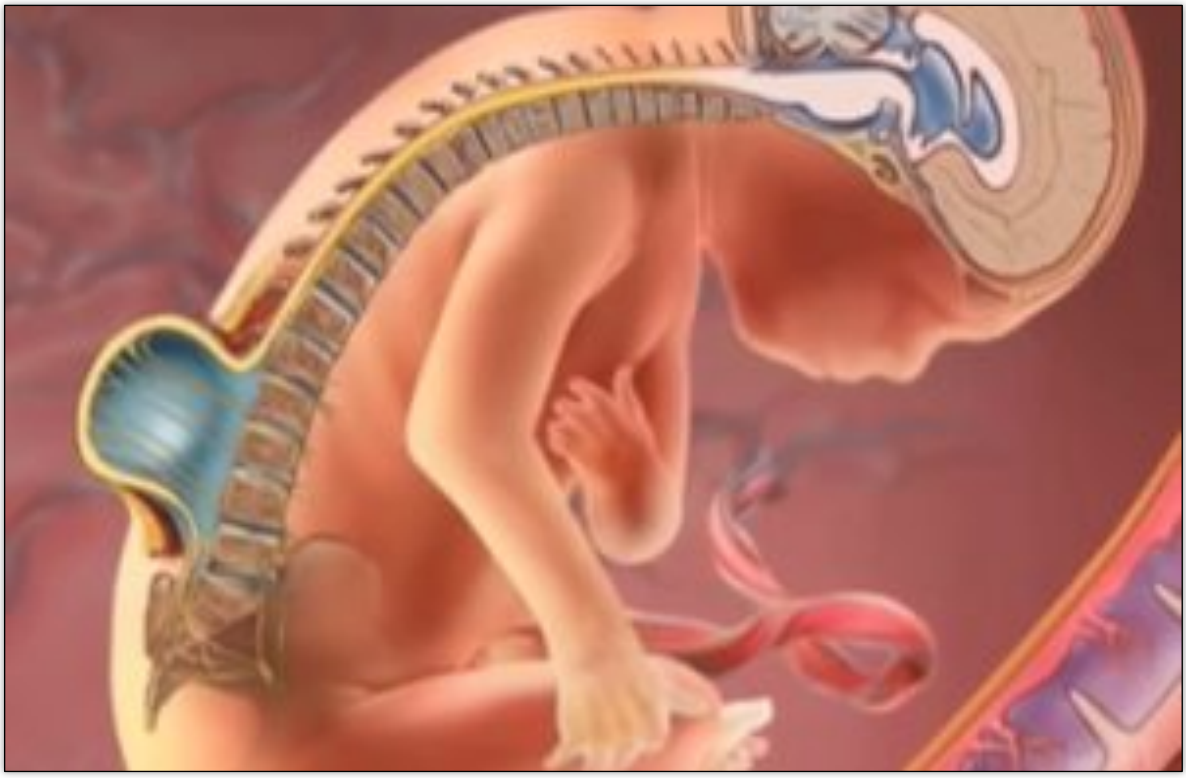
- Pathogenesis with special emphasis on the role of folate and alpha fetoproteins and their clinical significance.
- Definition and pathological changes in posterior fossa anomalies:
  - Arnold Chiari malformation.
- Hydrocephalus:
- Definitions of normal pressure hydrocephalus, noncommunicating hydrocephalus and communicating hydrocephalus - Pathophysiology and etiology.

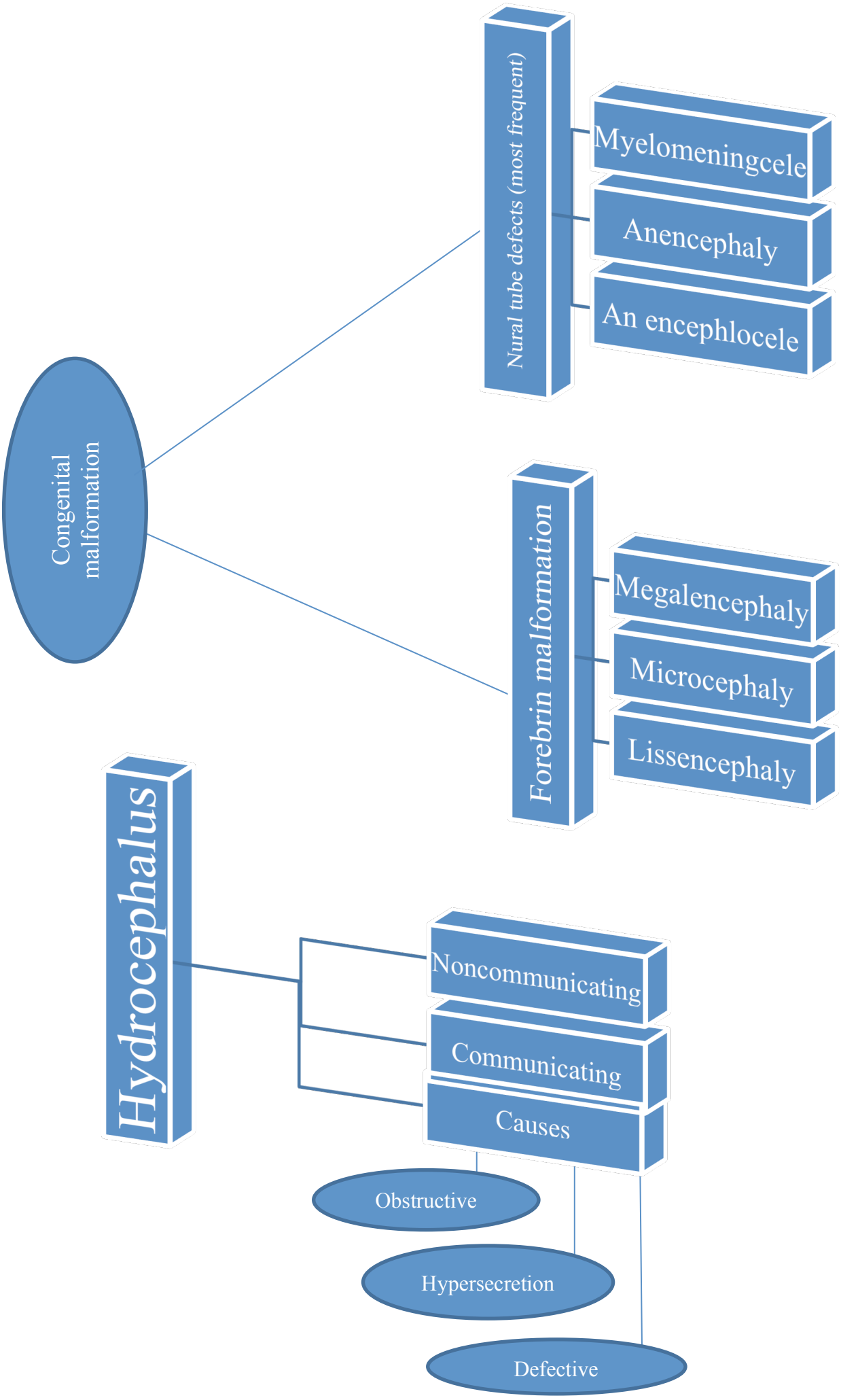
Take home messages:

- 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.

References:

Lecture, Robbins, First Aid, Kaplan Pathology Lecture Notes.




Congenital malformation
Nural tube defects (most frequent)
Myelomeningcele
Anencephaly
An encephlocele
Forebrin malformation
Megalencephaly
Microcephaly
Lissencephaly
Hydrocephalus
Noncommunicating
Communicating
Causes
Obstructive
Hypersecretion
Defective

Congenital Malformations:

- The incidence of CNS malformations, giving rise to mental retardation, cerebral palsy, or neural tube defects, is estimated at 1% to 2% (in the west).
- Malformations of the brain are more common in the setting of **multiple** birth defects.
- Prenatal[1] or perinatal[2] insults may either cause:
  - Failure of normal CNS development (they interfere with it)
  - Tissue destruction
- Because different parts of the brain develop at different times during gestation[3] (and afterwards), the timing of an injury will be reflected in the pattern of malformation. Earlier events lead to more severe phenotypes.

Cerebral palsy is caused by hypoxia (happens during delivery)

Amniocentesis: analyzing fluid; it's a medical procedure used in prenatal diagnosis of chromosomal abnormalities and fetal infections, and also used for sex determination in which a small amount of amniotic fluid, which contains fetal tissues, is sampled from the amniotic sac surrounding a developing fetus, than the fetal DNA is examined for genetic abnormalities.

What's the most crucial thing that plays a part in malformation of the brain?
The time at which the gestation occurs. And I can guess from the type of malformation, what's the time related to it.

- Although the pathogenesis and etiology of many malformations remain unknown, both genetic and environmental factors are clearly at play:
  - **CNS malformation** (may be due to genetic causes, prenatal infection, or exposure to teratogens (e.g., toxoplasmosis, alcohol, radiation)) **can be caused by Mutations** affecting molecules in pathways of neuronal and glial:
    - Development ▪ Migration ▪ Connection
  - Toxic compounds and infectious agents have teratogenic effects

What kind of vaccination is done to the girls to prevent malformations from happening? Rubella vaccine.

[1] Before birth; during pregnancy

[2] The period around childbirth, especially the five months before and one month after birth.

[3] The process of carrying or being carried in the womb between conception and birth.

Malformations:

- Neural Tube Defects
- Forebrain Malformations
- Posterior Fossa Anomalies
- Spinal Cord Abnormalities
- Perinatal Brain Injury
- Hydrocephalus

Now were able to diagnose it in pregnancy, and we can perform surgery on it.

Neural tube defect:

- Among the earliest stages in brain development is the formation of the neural tube, which gives rise to the ventricular system, brain and spinal cord.
- **Failure** of a portion of the neural tube to close, or reopening after successful closure, may lead to one of **several malformations.** All are **characterized by** abnormalities involving some combination of neural tissue, meninges, and overlying bone or soft tissues.
- Collectively, neural tube defects are the most frequent CNS malformations.
- **Folate deficiency** during the initial weeks of gestation is a risk factor; prenatal vitamins containing folate are aimed can reduce this risk by up to 70%.
- The combination of ultrasound and maternal screening for **elevated *α*-fetoprotein** has increased the early detection of neural tube defects
- The overall recurrence risk in subsequent pregnancies is 4% to 5%
- The most common defects involve the posterior end of the neural tube, from which the spinal cord forms.
- These defects can range from **asymptomatic bony defects (spina bifida occulta)** to severe malformation consisting of a flat, disorganized segment of spinal cord associated with an overlying meningeal outpouching. Which will be discussed below.

If we take a blood sample from the mother, we should be able to identify which type of neural deficit is happening in the fetus according to which enzymes are increased.

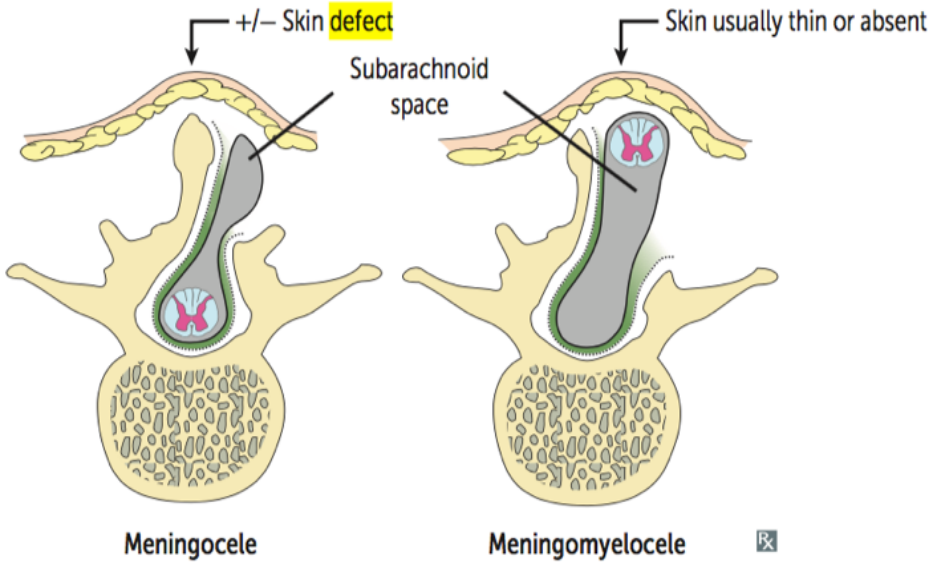
The development of this defect associated with low maternal folic acid levels early in pregnancy. Therefore, babies of mothers taking folate supplements prior to conception have a decreased risk of neural tube defects. Elevated a-fetoprotein in amniotic fluid and maternal serum is diagnostic. In utero ultrasound can confirm the presence of a deformity.

Diseases associated with Neural Tube defects:

Myelomeningocele:

An extension of CNS tissue through a defect in the vertebral column.

- They occur most commonly in the lumbosacral region.
- Patients have motor and sensory deficits in the lower extremities and problems with bowel and bladder control
- The symptoms derive from the abnormal spinal cord in this region, and are often compounded by infections extending from thin or ulcerated overlying skin.



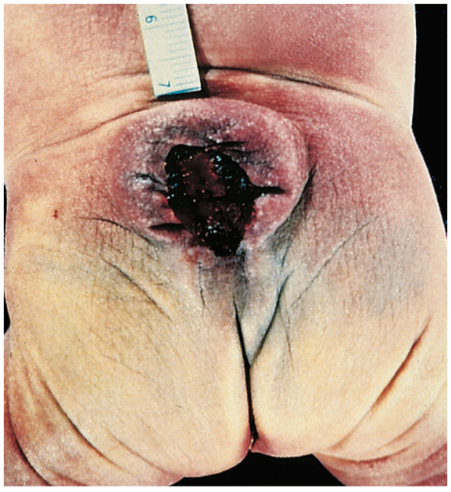


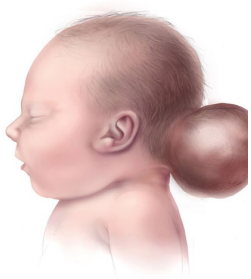
Figure 22–14 Myelomeningocele. Both meninges and spinal cord parenchyma are included in the cystlike structure visible just above the buttocks.

Anencephaly:

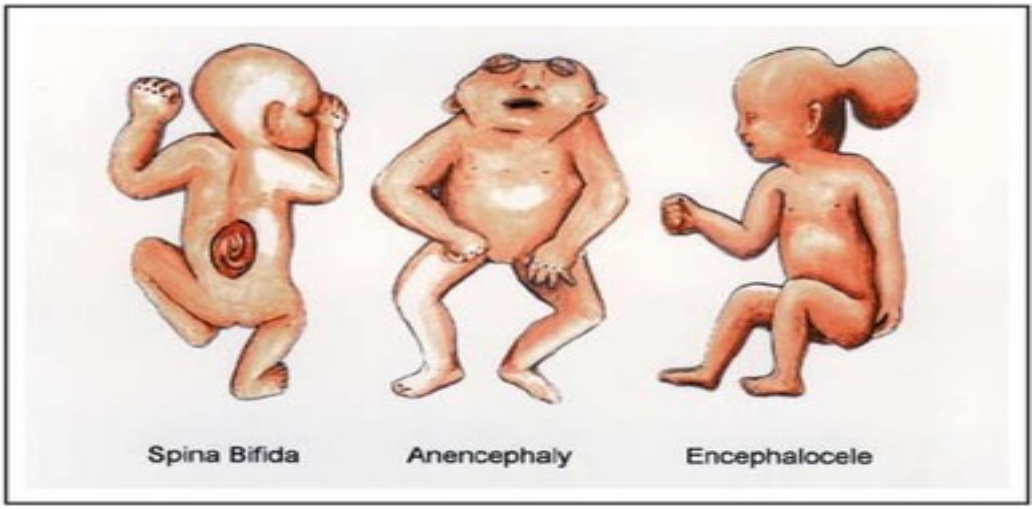
A malformation of the anterior end of the neural tube, with absence of the brain and top of skull.

Encephalocele:

A diverticulum of malformed CNS tissue extending through a defect in the **cranium.** It most often involves the occipital region or the posterior fossa. When it occurs anteriorly, brain tissue can extend into the sinuses.



Mylo: means brain (neural tissues)
Region affected: may occur at both ends, spinal bifida and the cerebral cortex.
Anencephaly: means no brain, and it's a fatal condition.



Forebrain Malformations:

The volume of brain in forebrain malformations might be:

- Abnormally large (***megalencephaly***)
- Small (***microencephaly***, *more common,* usually associated with a small head).

They can occur in a wide range of clinical settings, including:

- Chromosome abnormalities
- Fetal alcohol syndrome
- Human immunodeficiency virus 1 (HIV-1) infection acquired in utero

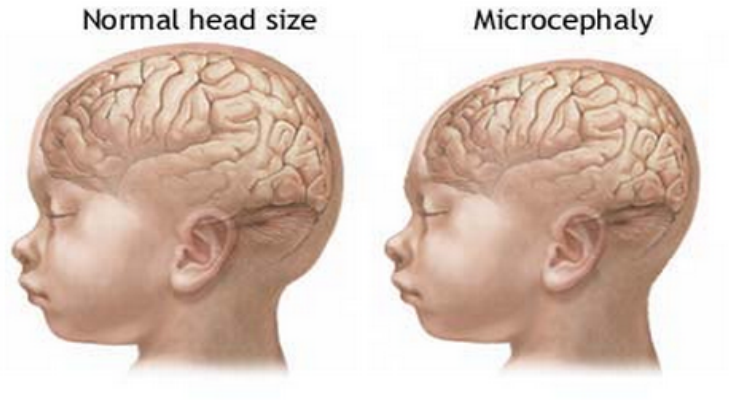
All causes are associated with:

- Decreased number of neurons of cerebral cortex.
- Disruption of normal neuronal migration and differentiation during development can lead to a disruption of the normal gyration and six-layered neocortical architecture

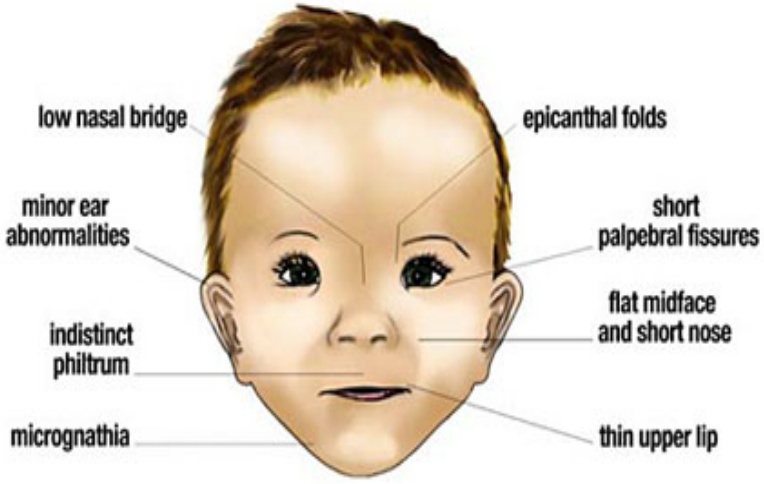
  How? During the early stages of brain development, as progenitor cells proliferate in the subependymal zone, the balance between cells leaving the progenitor population to begin migration to the cortex and those remaining in the proliferating pool affects the overall number of neurons and glial cells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

Why is time the important?

Because the different parts of the brain will devolve on a certain time, that's why the effect of early malformation will differ from the late ones.



Fetal alcohol syndrome



Leading cause of intellectual disability in the U.S. Newborns of alcohol-consuming mothers have ↑ incidence of congenital abnormalities, including pre- and postnatal developmental retardation, microcephaly, facial abnormalities (e.g., smooth philtrum, hypertelorism), limb dislocation, heart defects. Heart-lung stulas and holoprosencephaly in most severe form. Mechanism is failure of cell migration.

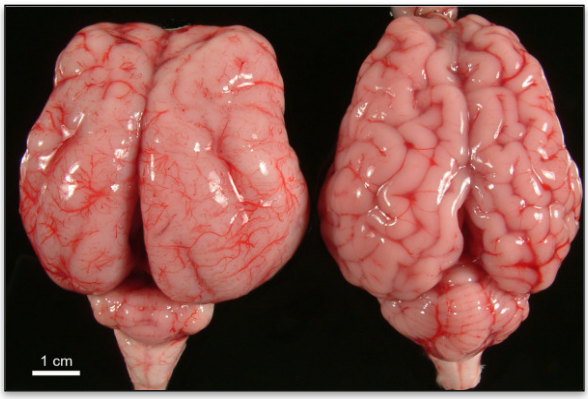
Various mutations in genes that control migration result in these malformations, which include the following:

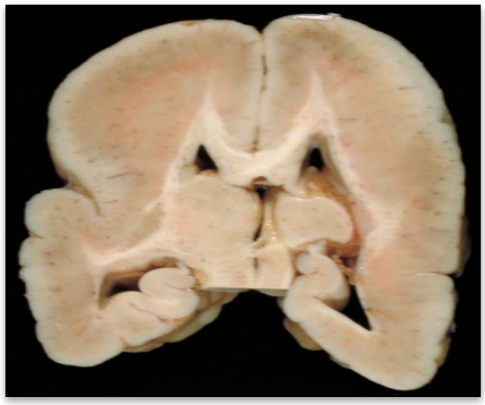
Lissencephaly (agyria):

Characterized by an absence of normal gyration and a smooth-surfaced brain. In case of more patchy involvement, it's called *pachygyria*

- The cortex is **abnormally thickened** and is usually only **four-layered.**
- **Single-gene** defects have been identified in some cases of lissencephaly.
- Cortical sulci are absent except, usually, for the Sylvian fissure.
- The cortex is thick and consists of the molecular and three neuronal layers (The deepest of these layers is the thickest and most cellular, 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.

No gyri in this brain, and sometimes even the sulci is not present, and it's due to what?
Failure of Migration.





Lisse in French: Soft
We have a brain that doesn't show the gyration.
If its involving all the brain (diffuse) we call it lissencephaly, and if its involving only patches, we call it pachygyria

Posterior Fossa Anomalies:

The most common malformations in this region of the brain result in either misplaced or absent cerebellum. Typically, these are associated with hydrocephalus.

Arnold-Chiari malformations:

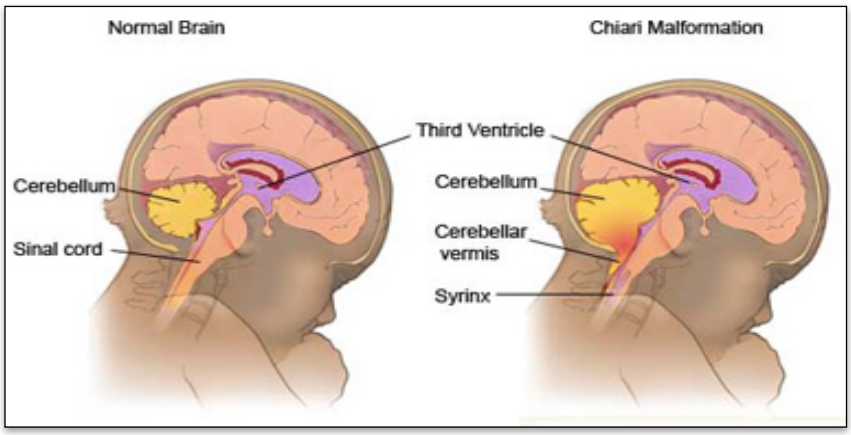
- ### Chiari type II malformation:

  Characterized by:

  - A small posterior fossa
  - A misshapen midline cerebellum
  - A lumbar myelomeningocele
  - Hydrocephalus
  - Downward extension of vermis through the foramen magnum

- ### Chiari type I malformation:

  - Milder.
  - Has low-lying cerebellar tonsils that extend through the foramen magnum.
  - Excess tissue in the foramen magnum results in partial obstruction of CSF flow and compression of the medulla, with symptoms of headache or cranial nerve deficits often manifesting only in adult life. Surgical intervention can alleviate the symptoms.



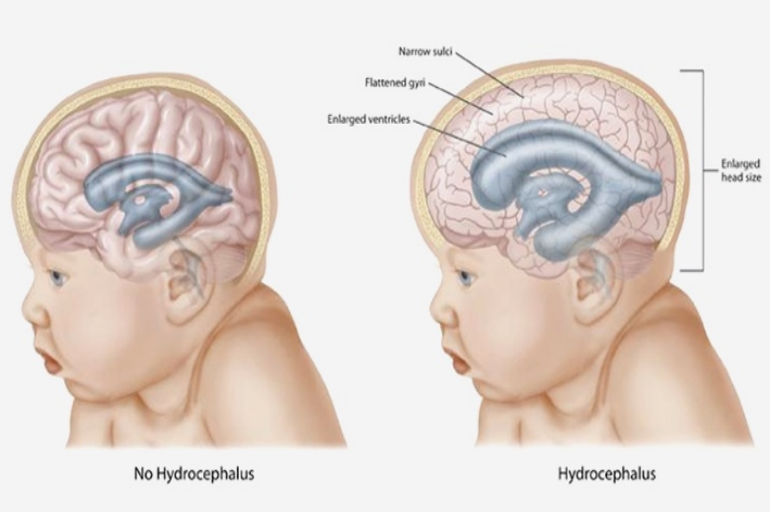
Hydrocephalus:

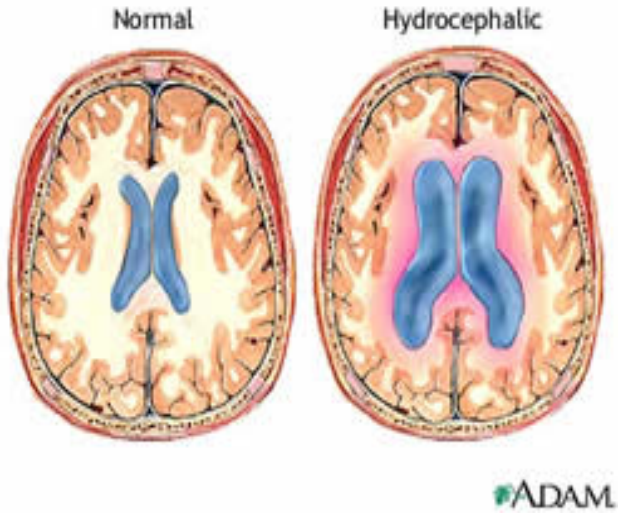
An abnormal accumulation of CSF in the ventricular system, which in turn may lead to an increased intracranial pressure (ICP).

- Most cases occur as a consequence of impaired flow or impaired resorption of CSF.
- In rare instances (e.g., tumors of the choroid plexus), overproduction of CSF may be responsible

Physiology of CSF:

- After being produced by the choroid plexus within the ventricles, cerebrospinal fluid (CSF) circulates through the ventricular system and exits through the foramina of Luschka and Magendie
- CSF fills the subarachnoid space around the brain and spinal cord, contributing to the cushioning of the nervous system within its bony confines
- The arachnoid granulations are responsible for the resorption of CSF
- The balance between CSF generation and resorption keeps the volume of this fluid stable





➢ When hydrocephalus develops in infancy before closure of the cranial sutures → enlargement of the head

➢ When Hydrocephalus develops after fusion of the sutures → expansion of the ventricles and increased intracranial pressure, without a change in head circumference.

Hydrocephalus: increase water in the brain due to CSF accumulation. There must be a balance between formation, resorption and circulation (flow).

Abnormalities in one of these three elements will lead to hydrocephalus, examples:

Increased formation of CSF, decrease resorption (abnormality in arachnoid) & obstructed post meningitis.

Types of hydrocephalus:

- **Noncommunicating hydrocephalus:**

  If there is an obstacle to the flow of CSF within the ventricular system, then a portion of the ventricles enlarges while the remainder does not. Caused by structural blockage of CSF circulation within ventricular system (e.g., stenosis of aqueduct of Sylvius; colloid cyst blocking foramen of Monro).

- **Communicating hydrocephalus:**

  The entire ventricular system is enlarged; here the cause is most often reduced resorption of CSF. (E.g., arachnoid scarring post-meningitis).

What can causes hydrocephalus?

1. **Hypersecretion of CSF**: (e.g. choroid plexus tumor)
2. **Obstructive hydrocephalus**
   - Obstruction of the foramina of (Monro e.g. colloid cyst, it's a benign tumor but can cause death to the patient)
   - Obstruction of the third ventricle (e.g. pilocytic astrocytoma)
   - Obstruction of the aqueduct (e.g. aqueductal stenosis or atresia and posterior fossa tumors)
   - Obstruction of the foramina of Luschka 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)
3. **Defective filtration of CSF:** postulated for low-pressure hydrocephalus (abnormal resorption)

Congenital Malformations and Perinatal Brain Injury Summary:

- Malformations of the brain can occur because of genetic factors or external insults.
- The developmental timing and position of the injury determine its pattern and characteristics.
- Various malformations stem from failure of neural tube closure, improper formation of neural structures, and altered neuronal migration.
- Perinatal brain injury mostly takes one of two forms: (1) hemorrhage, often in the region of the germinal matrix with the risk of extension into the ventricular system; and (2) ischemic infarcts, leading to periventricular leukomalacia.

Homework

Define Meningocele:

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

Define polymicrogyria:

Characterized by an increased number of irregularly formed gyri that result in a bumpy or cobblestone-like surface. These changes can be focal or widespread. The normal cortical architecture can be altered in various ways, and adjacent gyri often show fusion of the superficial molecular layer.

What is the difference between microcephaly and microencephaly?

Microcephaly: Small head

Microencephaly: Small Brain

Define hydrocephalus exvacuo:

Compensatory increase in CSF volume, following loss of brain parenchyma, as after infarcts or with degenerative diseases.

Check Your Understanding

MCQs:

1. **A 30 year old woman, G3, P2, is in the third trimester of pregnancy. She has noted minimal fetal movement throughout the pregnancy. A fetal ultrasound scan shows normal amniotic fluid volume and normally implanted placenta. Which of the following laboratory findings is most likely to be present in this woman?**
   A. 45, XX, t(14;21)(p11;q11) karyotype
   B. Elevated serum αfetoprotein level
   C. High cytomegalovirus IgM titer
   D. Hyperbilirubinemia with anemia

2. **Myelomeningocele is mainly a defect associated with:**
   A. Spinal cord
   B. Choroid plexus
   C. Vertebral column
   D. Anterior end of neural tube

3. **If a female gives birth to a baby with microenccephaly, the first infectious cause that would come to you mind would be:**
   A. HIV
   B. TB
   C. Brucella
   D. Toxoplasmosis

4. **What is the most frequent CNS malformations?**
   A. Neural tube defect
   B. Megalencephaly
   C. Microencephaly
   D. Microcephaly

5. **A pregnant female comes to you for her ultrasound. On the screen you can see that the brain is shrunken compared to the size it should be at this point of her pregnancy. You run an HIV test and it is (-). You revise the history and it turns out that she "enjoys" the occasional evening drink after work. Which of the following based upon this case would you expect to see within the fetus' brain:**
   A. Spina bifida
   B. A decrease in the number of neurons
   C. Anencephalus

6. **From the following name the malformation can be associated with lumbar spina bifida?**
   A. Arnold-Chiari malformation
   B. Lissencephaly
   C. Fetal alcohol syndrome
   D. Cranium bifidum

7. **On physical examination, a female newborn is found to have a defect in the lumbosacral region through which a segment of the spinal cord protrudes with an overlying meningeal outpouching. The mother did not receive prenatal care or routine prenatal screening. The abnormality seen in this newborn is associated with a maternal deficiency of which of the following substances?**
   A. Ascorbic acid.
   B. Cystathionine.
   C. Folic acid.
   D. Vitamin A.

1:B 2:C 3:A 4:A 5:B 6:A

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	هديل الغرير

قال صلى الله عليه وسلم: {من سلك طريقًا يلتمس فيه علمًا سهَّل الله له بهِ طريقًا إلى الجنة}

دعواتنا لكم بالتوفيق