

**Objectives:**

1. Define developmental defects and discuss etiological agents and pathogenesis of neurological developmental defects
2. List and discuss defects in closure of the neural tube.
3. Describe the pathology and clinical signs associated with syringomyelia.
4. Discuss and compare characteristics of the Arnold-Chiari malformation and the Dandy-Walker malformation.
5. For the following developmental defects of the cerebral hemispheres, define and discuss the pathology, and, when appropriate, the pathogenesis and clinical sequelae: Polymicrogyria, megalencephaly, microcephaly, heterotopias, holoprosencephaly, agenesis of the corpus callosum.

## I. General considerations

### A. General considerations

The differentiation of the nervous system continues for a very long period of time. In fact, differentiating cells are still present in the cerebellum at approximately one year post-natal age. This long period of differentiation provides the justification for considering "developmental defects" as disorders of growth resulting from interruption of the orderly sequence of development at any stage by any agent or disease category. Developmental defects are not only "developmental" in origin, but can arise from a vascular, traumatic, metabolic, toxic, nutritional, neoplastic or infectious etiology. Etiologic agents can either lead to interruptions of normal development or result in tissue destruction.

The etiology is actually unknown in most cases. Factors known to be associated with central nervous system malformations include:

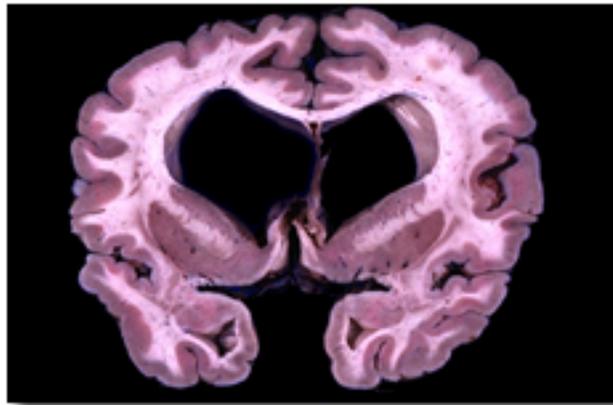
1. Chromosomal defects: The severity of malformations with the various chromosomal defects varies from case to case. In no instance is it really clear why specific abnormalities are associated with mental retardation
2. Certain infectious diseases are associated with specific sets of central nervous system malformations or disordered development. These include AIDS, syphilis, and the TORCH infections (toxoplasma, rubella, cytomegalovirus-CMV, herpes viruses) rubella, toxoplasmosis, syphilis, and cytomegalic inclusion virus.
3. Teratogenic drugs which induce developmental disorders include chemotherapeutic agents, medications such as anticonvulsant, and drugs of abuse (particularly alcohol - fetal alcohol syndrome).
4. Irradiation produces severe anomalies which depend on the developmental stage at the time of injury. In general, rapidly proliferating cell populations sustain the greatest damage.
5. Obstetrical complications in the perinatal period can arise from several sources, including trauma, vascular insufficiency, and infection. Varied lesions result.
6. Single gene inherited disorders
7. Hereditary "predisposition": e.g., individual differences in dilantin response; ethnic differences in neural tube defects.
8. Preexisting maternal disease, e.g. diabetes mellitus which is poorly controlled.

Two important concepts related to the pattern of defects are:

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- **Rapidly dividing or differentiating populations of cells are most susceptible to chemical and physical agents that disrupt DNA synthesis, e.g. x-rays.**
- **Many agents produce similar effects; the time of onset and extent of repair, rather than the nature of the insult, are the most crucial factors in determining the characteristics.**

The important and common developmental disorders will be reviewed first, and the anomalies at different levels of the nervous system (spinal cord, brainstem, cerebellum, and cerebral hemispheres) will be discussed. In addition to regional defects, hydrocephalus is an important problem.



**DD 01**  
Example of hydrocephalus

## II. Neural tube defects

Neural tube defects, which account for most CNS malformations, are due to failure of a portion of the neural tube to close, or reopening of a region after successful closure. Recall that the neural tube forms gradually from the neural plate by "zippering" in caudal and cephalad directions from the cervical region. The last portions of the neural tube to close are the anterior and posterior neuropores. The latter closes at about the 26th day of gestation. Midline defects, which are directly related to the lack of closure of the neural tube, are among the most common of central nervous system malformations. These defects, called dysraphic states, are probably related to both genetic and environmental causes. Since amniotic fluid contains increased alpha-fetoprotein content with "open" neural tube closure defects, prenatal diagnosis is possible. Folic acid supplementation before pregnancy and during its early stages markedly reduced the risk of neural tube defects in newborns. This finding led to the recommendation that women planning to become pregnant should take folic acid supplements.

1. Anencephaly - absence of the brain or of all parts except the basal ganglia, brainstem and cerebellum. The skull and meninges are often absent or defective. This defect is

possibly related to failure of closure of the anterior neuropore. Some affected infants live a few months.

2. Other midline defects.

a. Spina bifida - midline skeletal defect in spine

b. Myelomeningocele (meningomyelocele) - meninges and spinal cord protrude through overlying defect in the vertebral column. Most meningomyeloceles are found in a lumbosacral location. The majority of patients with meningomyeloceles also have hydrocephalus and Arnold-Chiari malformation. This is the most common nonlethal malformation in the spectrum of neural tube defects.

c. Encephalocele - meninges and brain tissue protrude through a skull defect.

d. Congenital dermal sinus - less serious but more common mid-line defect. Defects range from dimpling of skin over lumbosacral area to sinus tracts.



**DD 02**  
**Occipital encephalocele**

### III. Forebrain anomalies

Forebrain anomalies (Many of these are associated with mental retardation)

1. Polymicrogyria - increased number of small irregular gyri; not necessarily accompanied by mental retardation; commonly seen with the Arnold-Chiari malformation. The cortical architecture is abnormal, typically with 4 layers (instead of 6 layers normally found.)

2. Changes in the volume of brain tissue: megalencephaly (abnormally large volume) or microcephaly (brain smaller than normal without degenerative lesions). Microcephaly is more common and is associated with many inherited syndromes. Defects in five genes

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have been associated with familial forms of microcephaly. One of these genes, ASPM, is a major determinant of cerebral cortical size in several species.

3. Heterotopias - clusters of neurons in abnormal locations, usually in white matter; generally result from a failure of migration of nerve cells from the subependymal region to the cortex. These abnormal foci of neurons may cause seizures.

4. Holoprosencephaly - condition in which the cerebral hemispheres fail to divide properly. This condition, which is one of the most common developmental anomalies of the forebrain, involves total or partial lack of division of telencephalic vesicles, optic vesicles, and/or olfactory vesicles. Most cases are sporadic but familial cases are not rare, with a clear pattern of autosomal dominant inheritance. One mutation involves the sonic hedgehog (SHH) gene, which produces an intercellular signaling molecule.

5. Agenesis of the corpus callosum - may occur as an isolated anomaly without any clinical dysfunction, but this condition is often associated with other malformations.



**DD 03**  
Example of Polymicrogyria

#### **IV. Posterior fossa anomalies**

1. Arnold-Chiari malformation - small posterior fossa

The term "Chiari malformation" encompasses a complex of abnormalities of the brainstem and cerebellum. Four types have been described. Type II, called the Arnold-Chiari malformation, is the most common and is almost always associated with polymicrogyria, meningocele, and hydrocephalus. There is a probable pattern of multifactorial inheritance. The Arnold-Chiari malformation is characterized by:

a) misshapen midline cerebellum with downward extension of cerebellar vermis through foramen magnum

- b) elongation of medulla, pons and 4th ventricle, with kinking of medulla.
- c) "beak"-shaped malformation of colliculi
- d) aqueductal stenosis, leading to hydrocephalus



**DD 04**

Example of radiology showing Arnold-Chiari malformation

2. Dandy-Walker malformation - large posterior fossa

Pathological characteristics include:

- a) malformation of cerebellar vermis with a midline cyst replacing parts of the vermis
- b) lateral displacement of cerebellar hemispheres by 4th ventricle



**DD 05**

Example of Pathological changes in Dandy-Walker syndrome, showing cyst between the cerebellar hemispheres.

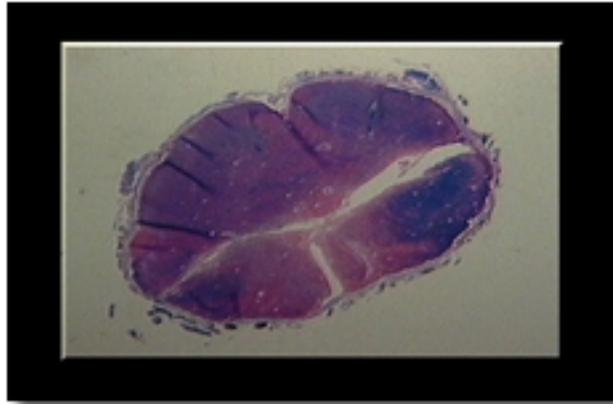
**V. Syringomyelia**

Syringomyelia (may affect individuals at any age)

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- **commonly occurs at cervical levels; clefts may extend into the brainstem**
- **can be caused by a variety of etiologies besides defective development including hemorrhage.**

Clinically, the patient often presents with loss of pain and temperature symmetrically in the hands as well as wasting of the hand muscles. This is due to encroachment of the cystic cavity in the cord on the anterior commissure which carries pain fibers and the anterior horns which contain the motor neurons which innervate the hand.



**DD 06**

**A cleft in the spinal cord is shown as an illustration of syringomyelia.**