

Neuroscience I
Pathology of CNS
malformation, brain edema and
parenchymal injury

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MALFORMATIONS AND DEVELOPMENTAL DISORDERS

the pathogenesis and etiology of many CNS malformations remain unknown, both genetic and environmental influences appear to be involved. The causal relationship between these genetic alterations and the pathogenesis of the malformations is the subject of active research. Besides genetic factors, many toxic compounds and infectious agents also have teratogenic effects and may cause brain malformations.



Congenital abnormalities are among the leading causes of infant morbidity and mortality and fetal loss. The leading sites of congenital abnormalities are the skeleton, skin, and brain.

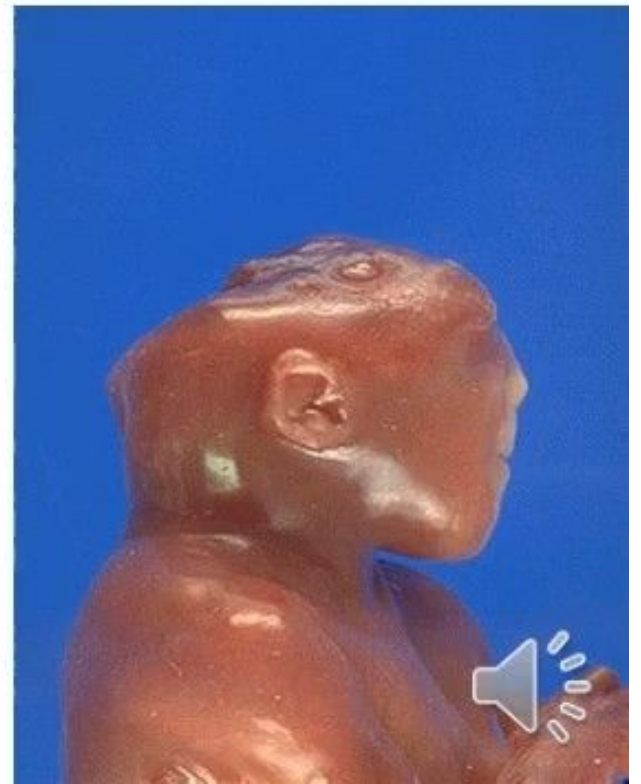


Neural Tube Defects

Neural tube defects are midline malformations that involve some combination of neural tissue, meninges, and overlying bone or soft tissue; collectively, they are the most common CNS malformations. Two distinct pathogenic mechanisms are contributory: (1) failure of neural tube closure (e.g., anencephaly and myelomeningocele); and (2) primary bony defects that are caused by abnormal axial mesoderm development and lead to secondary CNS abnormalities (e.g., encephalocele, meningocele, and spina bifida).



Anencephaly is absence of the fetal cranial vault. Exposure of cerebral tissue to amniotic fluid precludes brain development. Anencephaly is a form of neural tube defect that is typically an isolated birth defect that is not related to chromosomal abnormalities. Embryologically, there is failure of the anterior neuropore to close, resulting in failure of the calvaria to form (called acrania). The lack of a protective vault leaves any developing brain vulnerable to destruction.



The incidence of anencephaly, has been reported to occur as frequently as 1 to 5 in 1000 live births in the past. However, dietary folic acid supplementation by mothers-to-be before and during pregnancy can reduce the incidence of such birth defects. The rate of anencephaly is now less than 1 in 10,000 live births in some places.



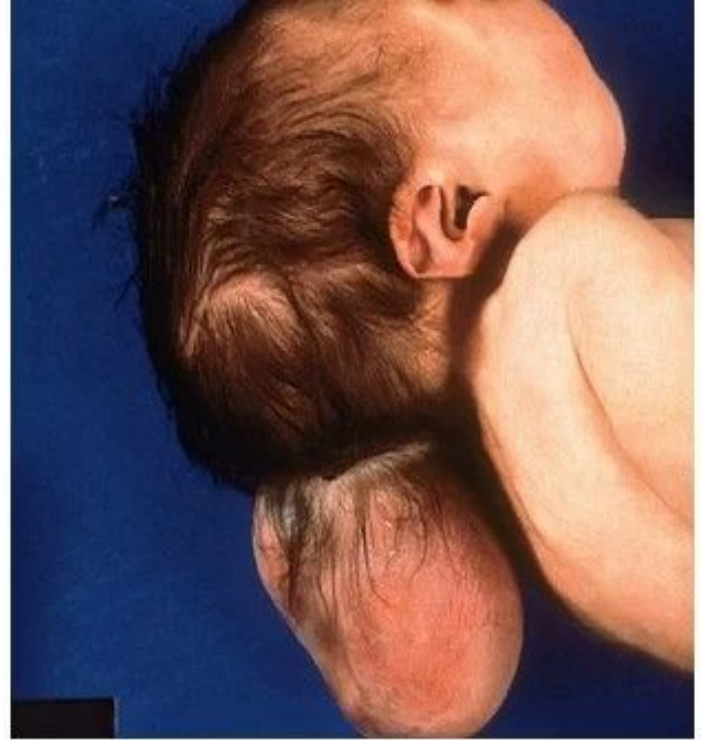
Myelomeningocele

Myelomeningocele is a severe form of spina bifida in which the spinal cord and nerves develop outside of the body and are contained in a fluid-filled sac that is visible outside of the back area. These babies typically have weakness and loss of sensation below the sac. This can result in muscle weakness and/or paralysis, bowel and bladder problems, excessive fluid on the brain (hydrocephalus), change in positioning of the brain (Chiari Malformation), seizures, and orthopedic conditions (scoliosis, hip problems, and foot deformities). Myelomeningocele affects about 1 in every 1,000 babies



Encephalocele refers to an extrusion of malformed brain tissue through a midline defect in the cranium. It most often occurs in the occiput, although nasofrontal variants involving the orbit, ethmoid, or cribriform plate (sometimes misleadingly referred to as a “nasal glioma”) also are seen.

Spinal dysraphism or spina bifida (the most common neural tube defects) may be an asymptomatic bony defect (spina bifida occulta) or a severe malformation with a flattened, disorganized segment of spinal cord, associated with an overlying meningeal outpouching



Forebrain Anomalies

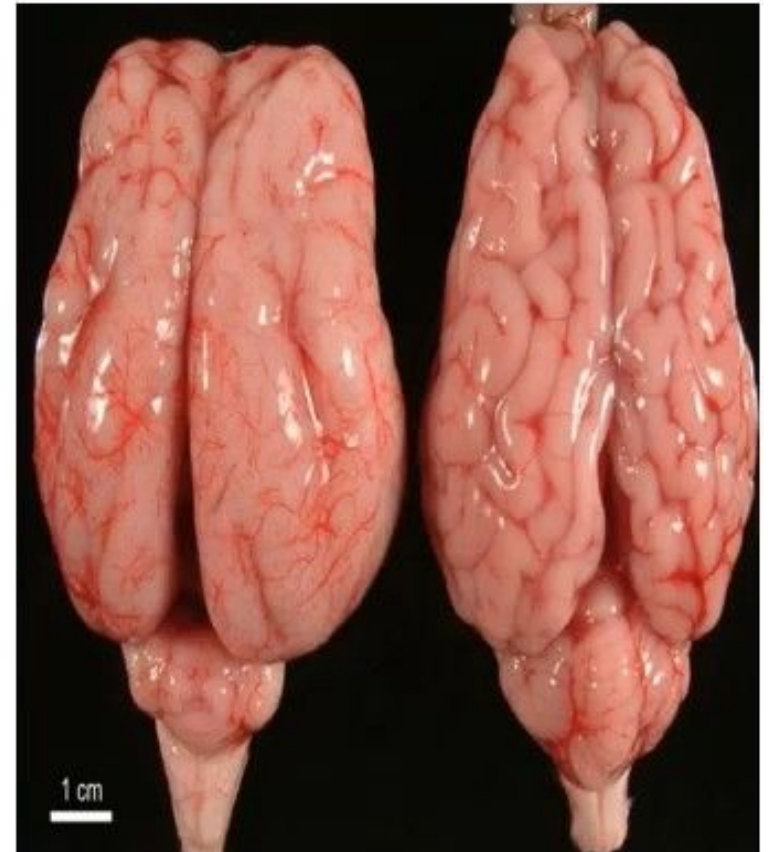
Abnormalities in the generation and migration of neurons result in malformations of the forebrain that may be focal or involve entire structures. range of different anatomic malformation patterns has been defined. Recently, it has become clear that many of these patterns are caused by mutations in genes that are required for proper cerebral development.



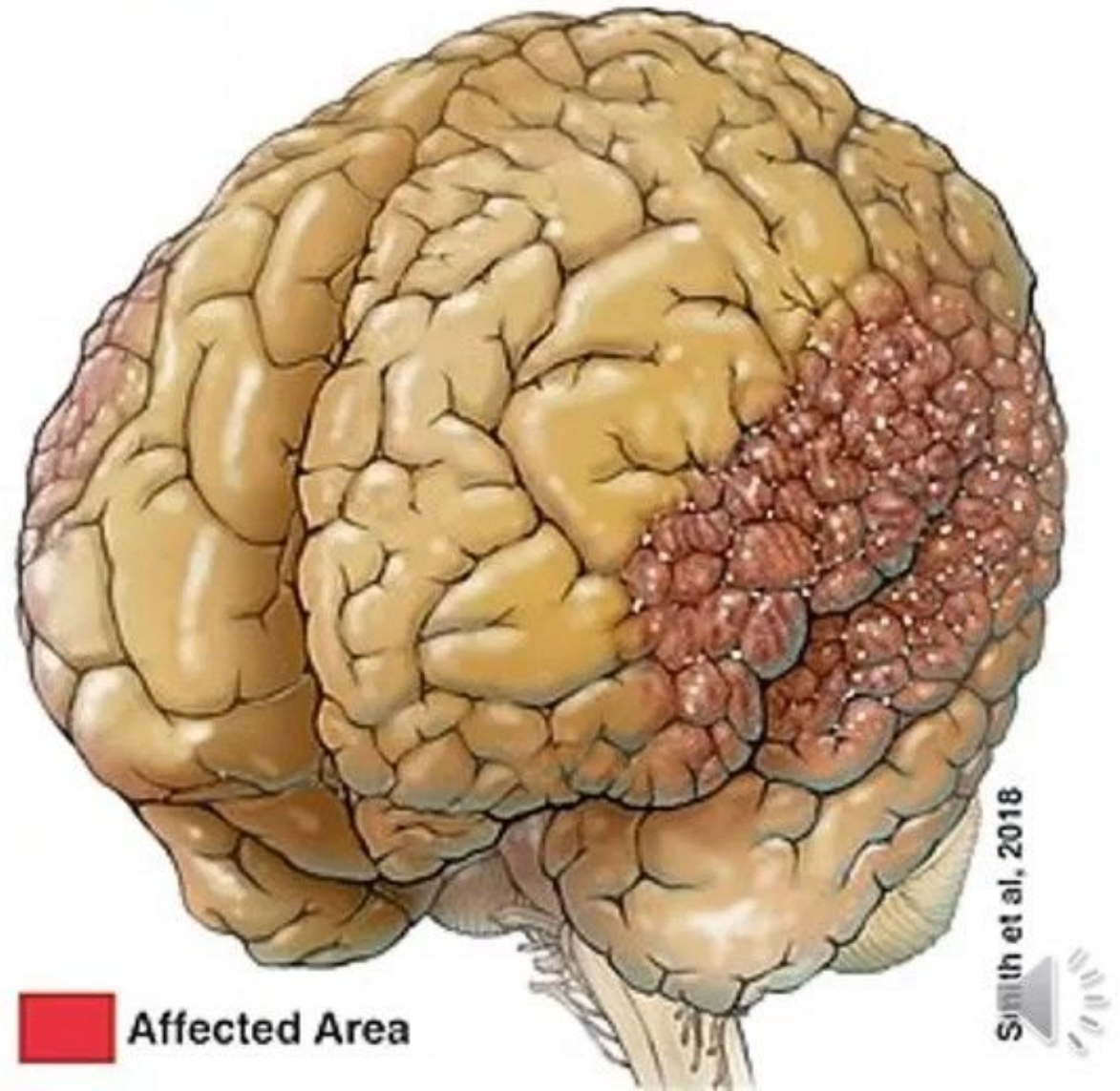
The volume of brain may be abnormally large (megaloencephaly) or abnormally small (microencephaly). Microencephaly, by far the more common of the two, is typically accompanied by a small head circumference. It is associated with a number of conditions, including chromosome abnormalities, fetal alcohol syndrome, and viral infection acquired in utero (e.g., with human immunodeficiency virus 1 [HIV-1] or Zika virus). It is postulated that the underlying anomaly is a reduction in the number of neurons that reach the neocortex, which leads to a simplification of gyral folding, a mechanism supported by experimental results in mouse models.



Lissencephaly is a malformation characterized by reduction in the number of gyri, which in the extreme case may show no gyral pattern (agyria). Two general patterns are observed, a smooth-surface form (type 1), and a rough- or cobblestone-surface form (type 2). In general, type 1 forms are associated with mutations that disrupt mechanisms involved in cell migration, such as mutations in the cytoskeletal “motor” proteins that drive migration of neuroblasts. In contrast, type 2 lissencephaly is most commonly associated with genetic alterations that disrupt the “stop signal” for migration.



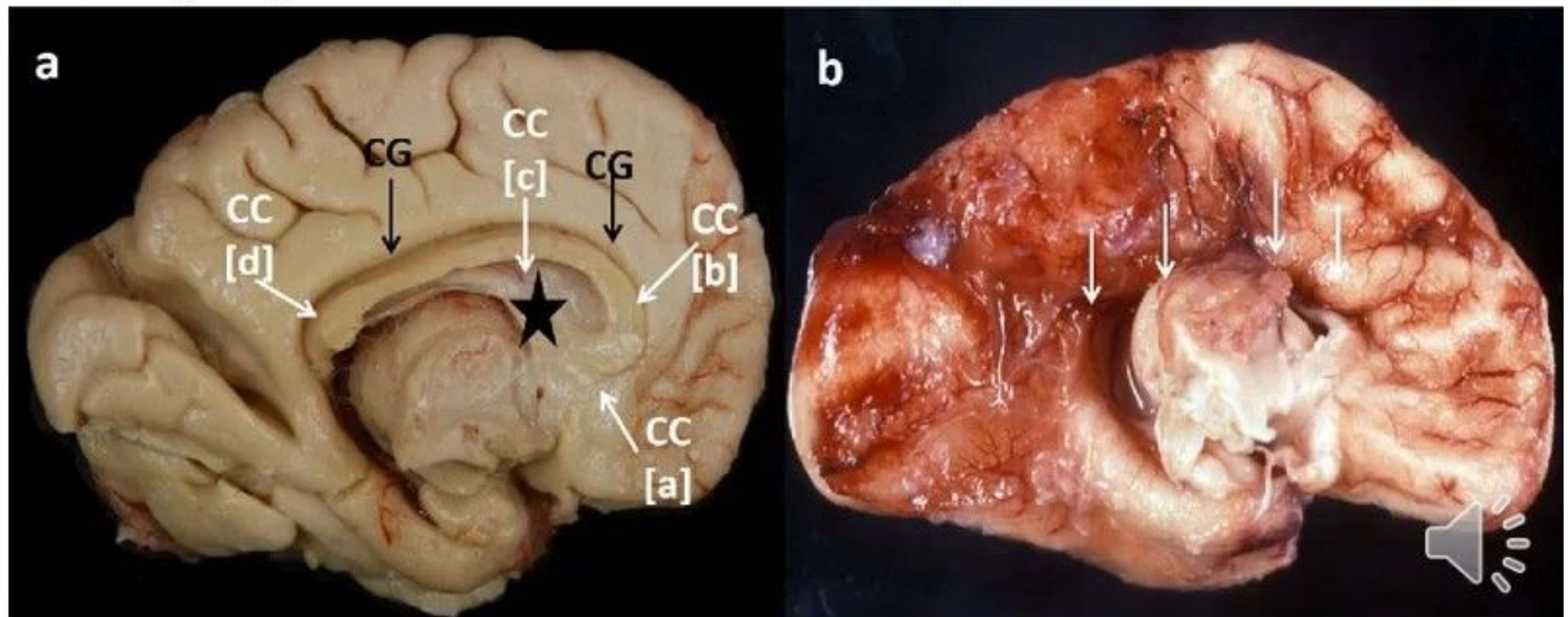
Polymicrogyria is characterized by numerous small, irregularly formed cerebral convolutions with shallow sulci. The cerebral cortex is composed of four or fewer layers (instead of the normal six layers), with fusion of the molecular layers between gyri.



Neuronal heterotopias are a group of migrational disorders defined by collections of subcortical neurons in inappropriate locations along the pathway of migration.

lprosencephaly is a spectrum of malformations characterized by incomplete separation of the cerebral hemispheres across the midline.

Agensis of the corpus callosum, a relatively common malformation, is the absence of the white matter bundles that carry cortical projections from one hemisphere to the other



Posterior Fossa Anomalies

A distinct set of malformations primarily affect the brainstem and the cerebellum, which often show dramatic changes in size and shape. These may be accompanied by morphologic changes in other regions of the brain

MORPHOLOGY

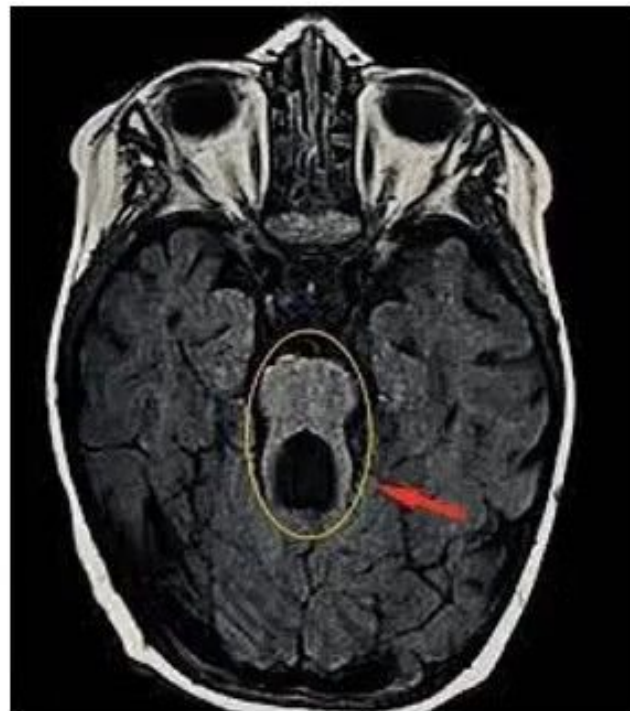
- Arnold-Chiari malformation (Chiari type II malformation) consists of a small posterior fossa, a misshapen midline cerebellum with downward extension of vermis through the foramen magnum , and, almost invariably, hydrocephalus and a lumbar myelomeningocele



- **Chiari type I malformation** is a less severe disorder in which low-lying cerebellar tonsils extend down into the vertebral canal. It may be a silent abnormality or may become symptomatic because of impaired CSF flow and medullary compression; if present, these symptoms can usually be corrected by neurosurgical intervention.
- **Dandy-Walker malformation** is characterized by an enlarged posterior fossa. The cerebellar vermis is absent or present only in rudimentary form in its anterior portion; in its place is a large midline cyst that is lined by ependyma and is contiguous with leptomeninges on its outer surface. This cyst represents the expanded, roofless fourth ventricle in the absence of a normally formed vermis. Dysplasias of brainstem nuclei are commonly found in association with Dandy-Walker malformation.

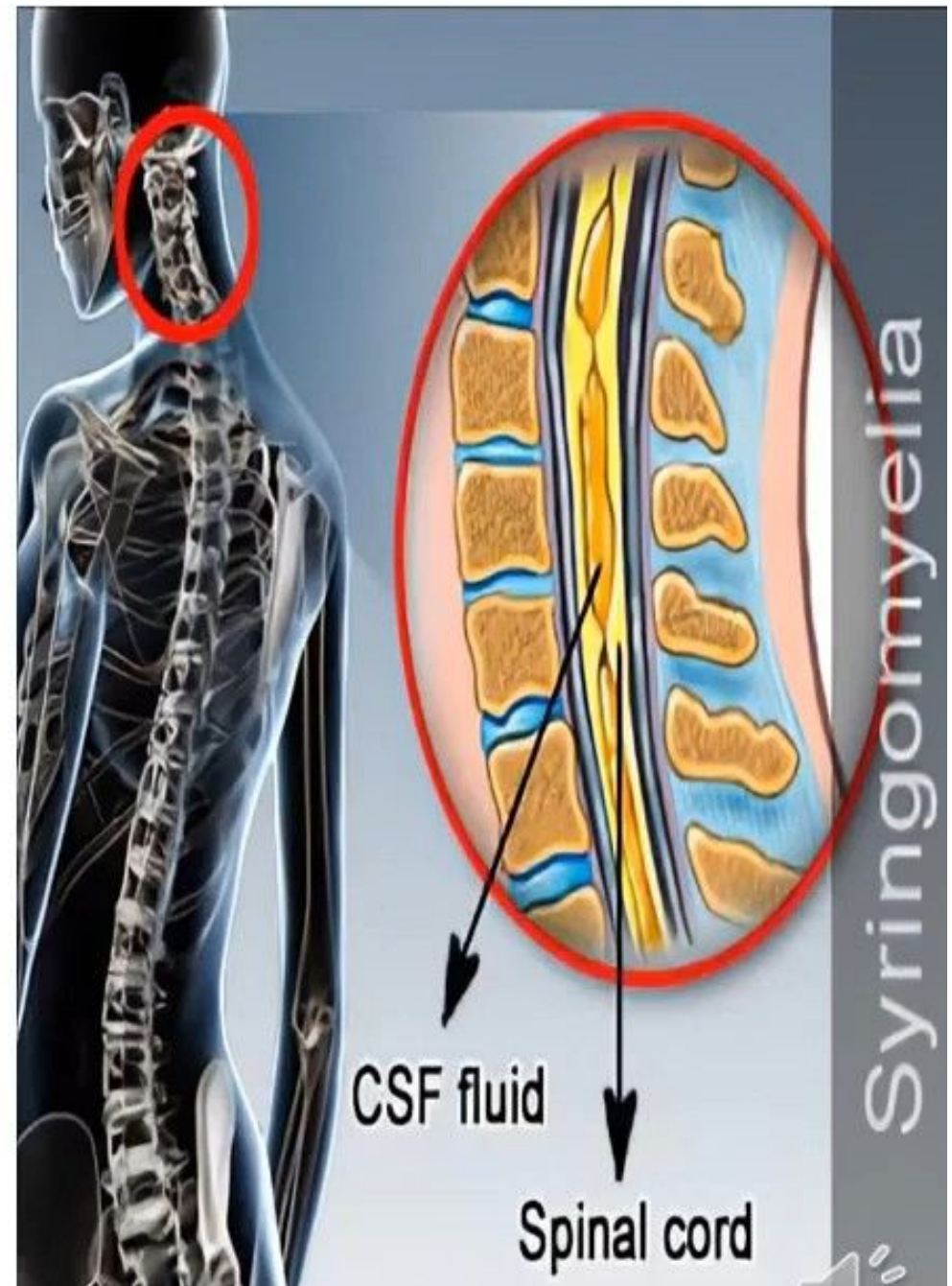


- Joubert syndrome and related disorders share hypoplasia of the cerebellar vermis with apparent elongation of the superior cerebellar peduncles and an altered shape of the brainstem; together these changes give rise to the “molar tooth sign” on imaging. This group of malformations has been found to be caused by diverse mutations affecting genes that encode components of the primary (nonmotile) cilium.



Syringomyelia and Hydromyelia

These disorders are characterized by expansion of the ependyma-lined central canal of the cord (hydromyelia) or by the formation of a fluid-filled cleftlike cavity in the inner portion of the cord (syringomyelia, syrinx) that may extend into the brainstem (syringobulbia).



syringomyelia may be associated with a Chiari malformation; it may also occur in association with intraspinal tumors or following traumatic injury. In general, the histologic appearance is similar in all of these conditions, with destruction of the adjacent gray and white matter, surrounded by dense reactive gliosis. The disease generally becomes manifest in the second or third decade of life. The distinctive symptoms and signs of a syrinx are the isolated loss of pain and temperature sensation in the upper extremities because of disruption of the crossing anterior spinal commissural fibers of the spinal cord.



CEREBRAL EDEMA, HYDROCEPHALUS, RAISED INTRACRANIAL PRESSURE, AND HERNIATION

The brain and the spinal cord are encased and protected by the rigid skull, dural reflections, and the bony spinal canal. The pressure within the cranial cavity may rise in any one of three commonly observed clinical settings: generalized brain edema, increased CSF volume, and focally expanding mass lesions. Depending on the degree and rapidity of the pressure increase and the nature of the underlying lesion, the consequences range from subtle neurologic deficits to death.

