Developmental Neuropathology

EARLY

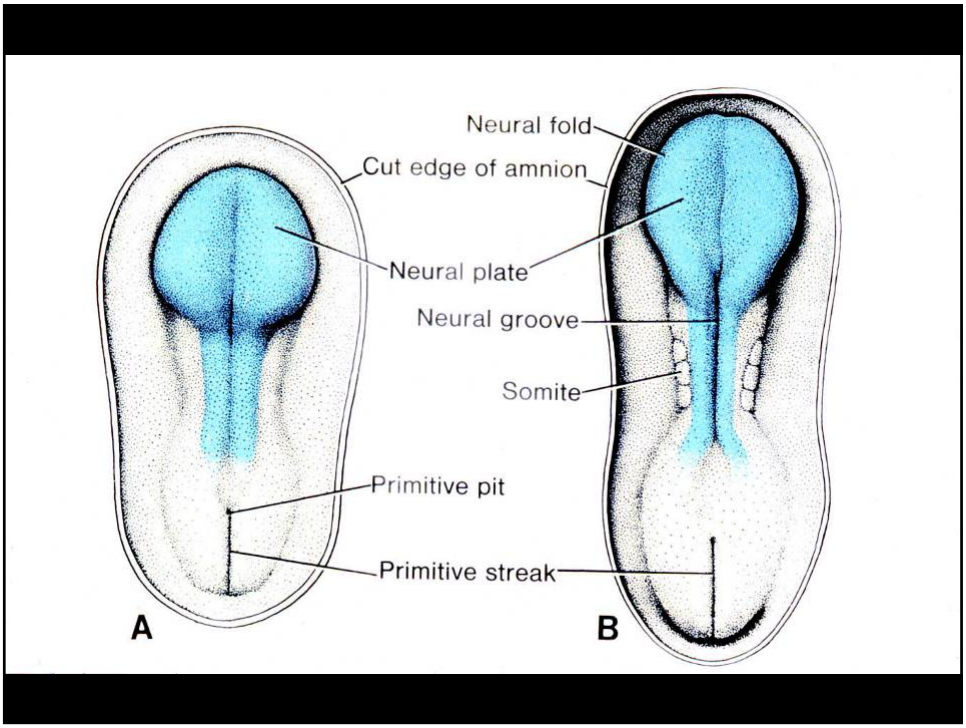
Anterior closure E26
Posterior closure E28

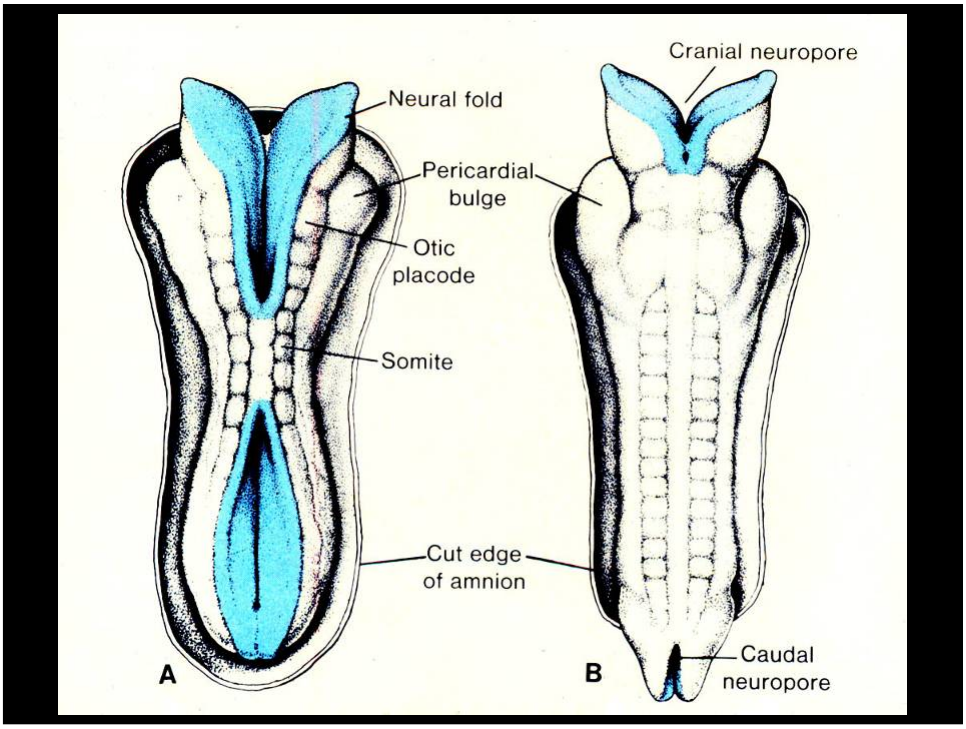
Anencephaly E16-E26
Spina Bifida
Holoprosencephaly (anterior midline closure)

MID-GESTATION

Neuronal migration
Gyral formation

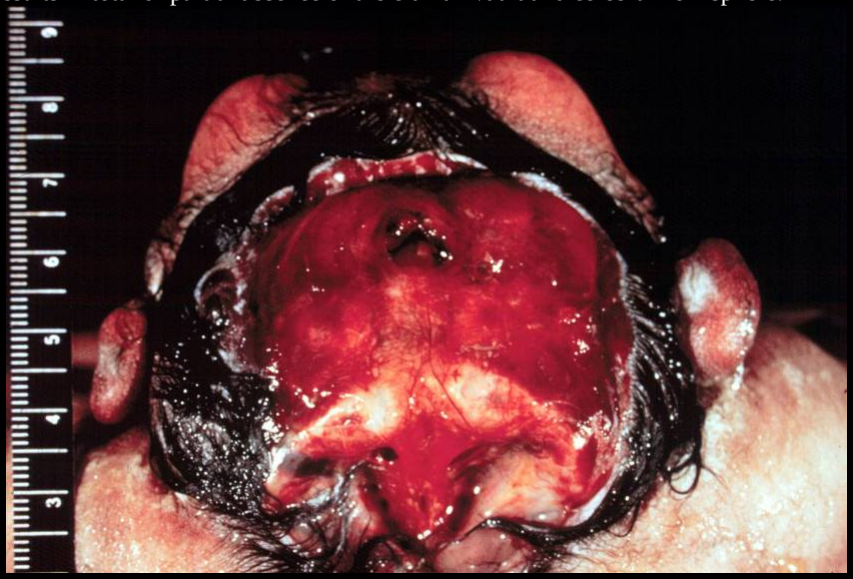
Heterotopias
Macro/Microgyria
Lissencephaly

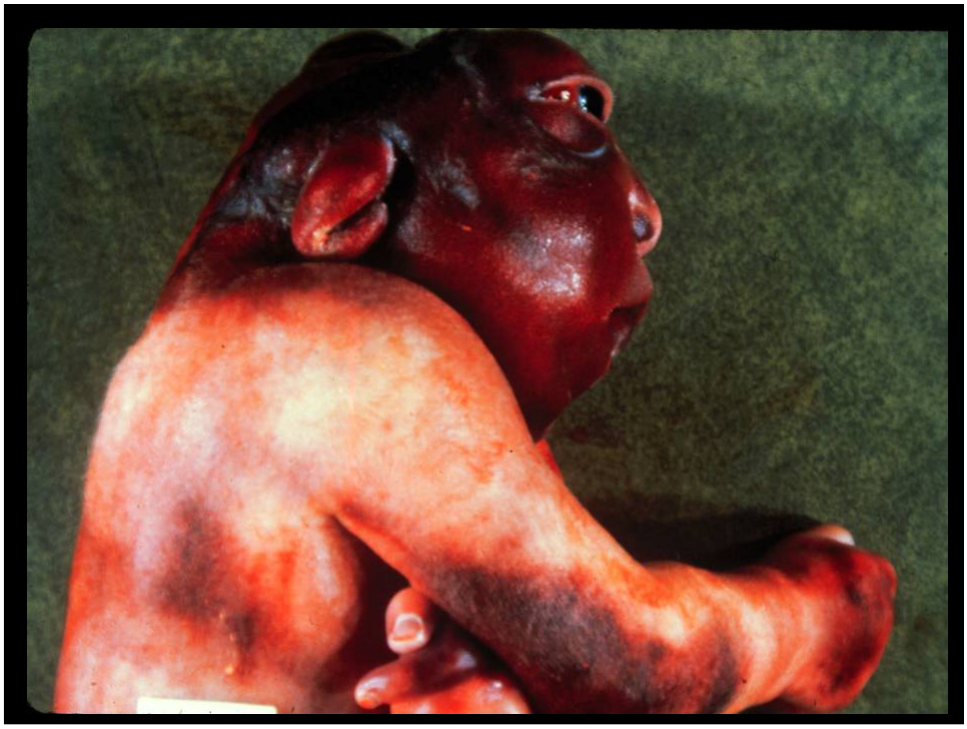




Anecephaly

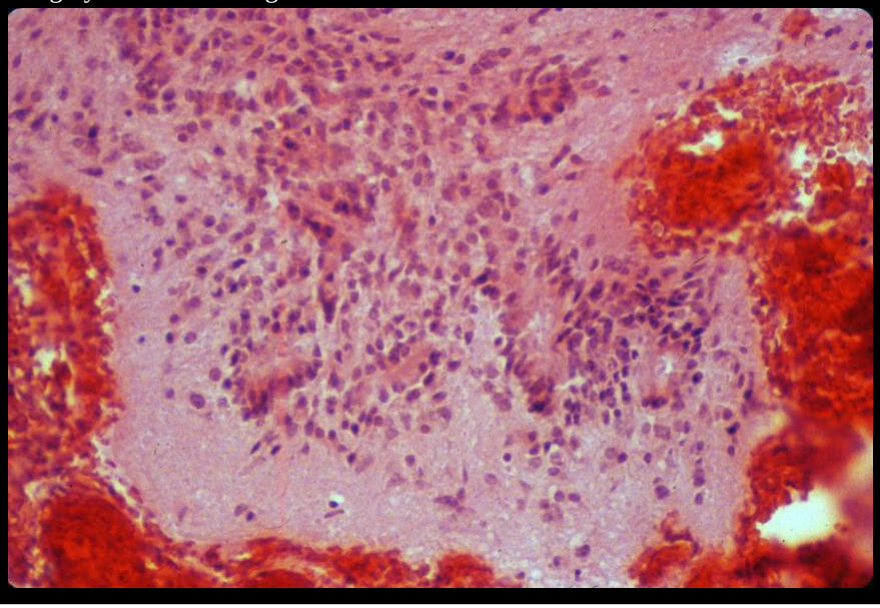
A failure of anterior neural tube closure due to injury/defect at 18-26 days of gestation. Results in total or partial absence of the cranial vault and cerebral hemisphere.

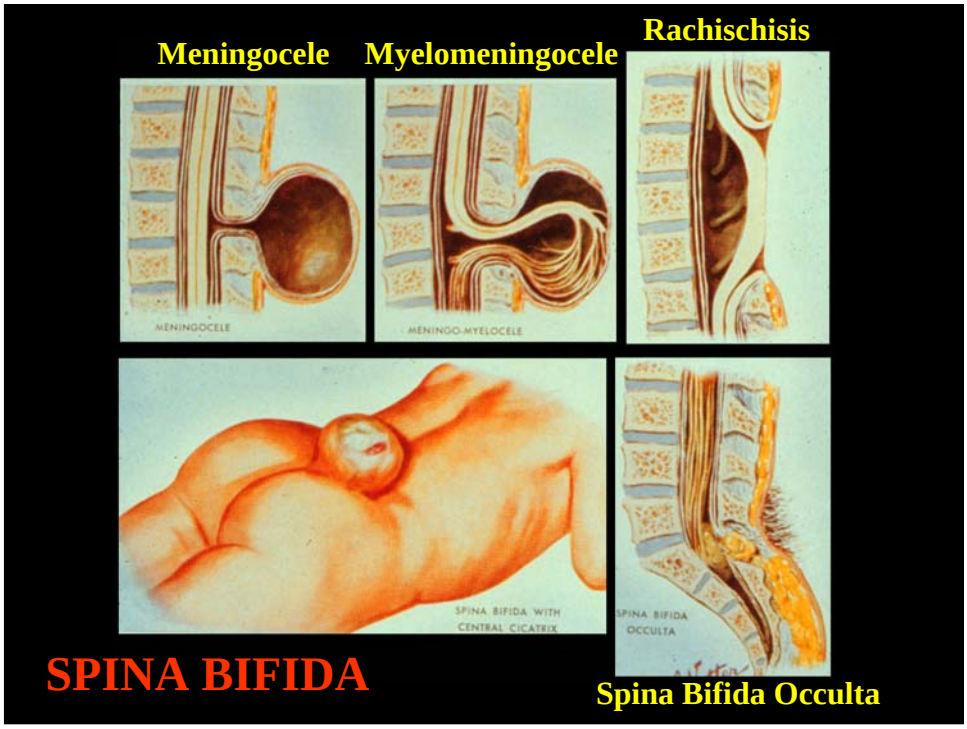




‘Area Cerebrovasculosa’ in anencephaly

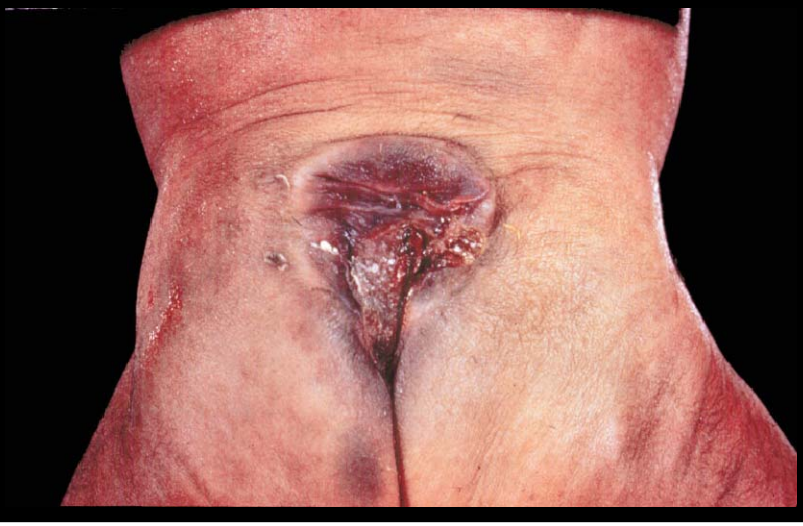
The cranial contents consist of a mass of disorganized neuroepithelial tissue covered by a highly vascular meninges.





Myelomeningocele in sacral region

An open spinal cord defect containing dysplastic spinal cord, nerve roots, and leptomeninges. Often results in lack of spinal cord function below the defect. Patients have reduced ability to walk/wheelchair bound, little or no bowel and/or bladder control, frequent surgical interventions to minimize effects of hydrocephalus.



Pathogenesis of Anencephaly/NTDs

• Neural tube defects (NTDs) are very common malformations, ~1/1000 birth incidence in American Caucasians (varies among ethnic groups), second most common defect after congenital heart defects. Anenecephaly and myelomeningocele are the most common NTDs.

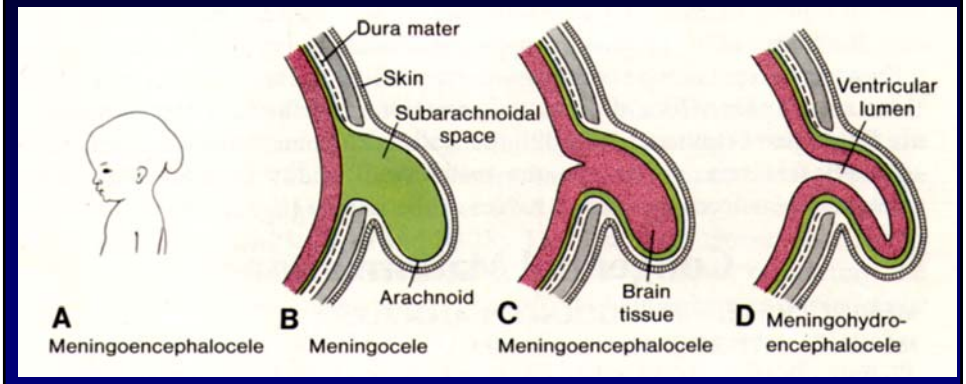
• Folic acid deficiency is a well established nutritional factor that increases incidence of neural tube defects. Folic acid is obtain from diet in green leafy vegetables. Prophylactic supplementation in women of childbearing ages in endemic regions/populations with poor nutrition. Folate metabolism genes/autoantibodies?

• Environmental teratogens/factors - maternal diabetes and obesity, maternal use of anticonvulsants. Many others suspected.

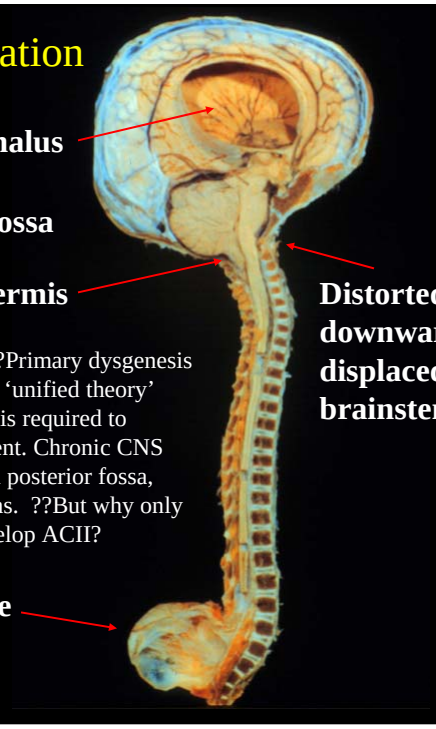
• Genetic factors may play a role, i.e. increased risk for recurrence in subsequent pregnancies if have affected child (2-5%, ~50x increased risk). Frequent association of NTDs in trisomies 13 and 18. In patients with NTDs, 6.5% (range 5-17%) have chromosomal anomalies.

• Multiple genes (80-100) in rodents give rise to NTDs - genes key for closure of neural tube. Penetrance of defect depends on genetic background, i.e. multifactorial inheritance. None of these gene loci are a major gene for NTDs in humans.

Encephaloceles



Arnold-Chiari Malformation (Chiari type II)



Hydrocephalus

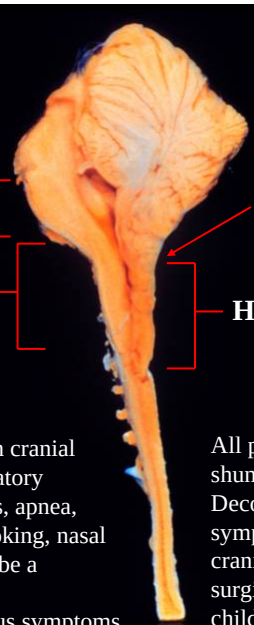
Small posterior fossa

Herniation of cerebellar vermis

Distorted and downwardly displaced brainstem

Variety of pathogenetic theories put forth: ?Primary dysgenesis of the posterior fossa mesoderm, others. A 'unified theory' invokes concept that ventricular distension is required to induce both neural and calvarial development. Chronic CNS leak from open spinal defect leads to small posterior fossa, eventual hindbrain crowding and herniations. ??But why only some patients with open spinal defects develop ACII?

Sacral Myelomeningocele



Flattened pons

Position of foramen magnum

Flattened and herniated medulla

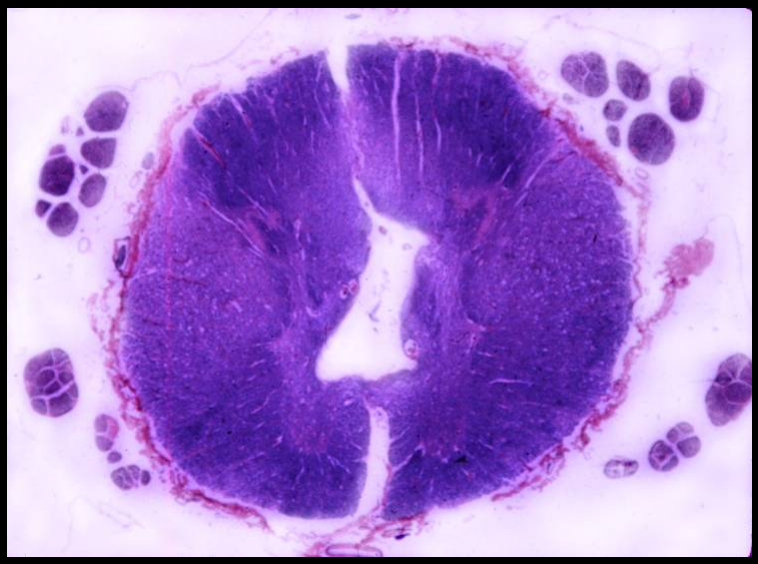
Herniated cerebellum

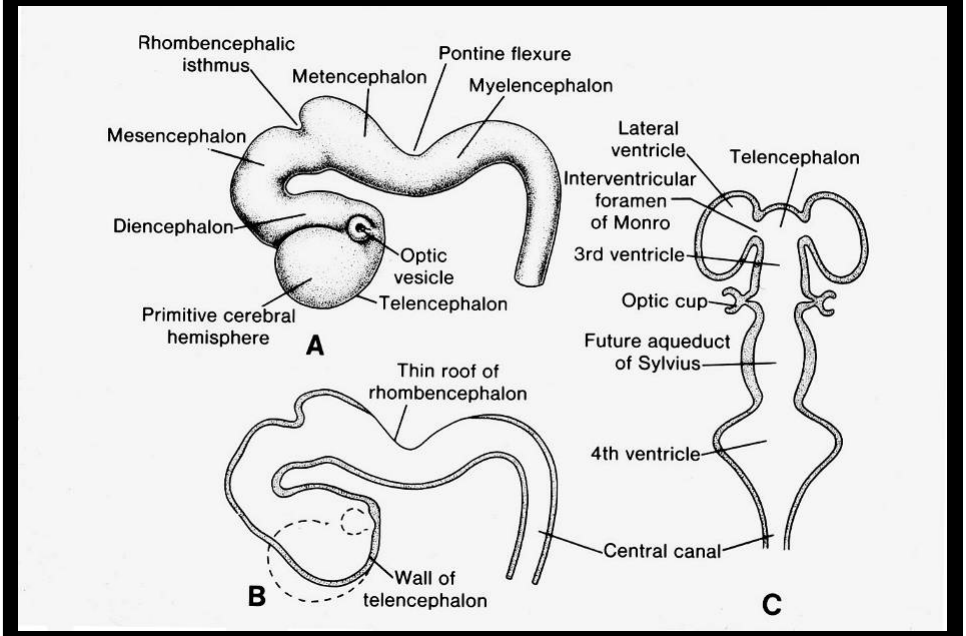
Children < 2 years of age present with cranial nerve and brainstem signs, e.g. respiratory problems, vocal cord paresis/paralysis, apnea, neurogenic dysphagia (aspiration, choking, nasal regurgitation, etc.), weight loss. Can be a neurosurgical emergency.
Children >2 years of age with insidious symptoms, e.g. cervical myelopathy (upper extremity weakness, spasticity), ataxia, occipital headache.

All patients are treated with CNS shunts to prevent hydrocephalus. Decompression surgery if become symptomatic from brainstem and cranial nerve signs - 15-23% surgical mortality rate in young children. Up to 15% of symptomatic CM II patients die by age 3 years.

Syringomyelia

Tubular cavitation of the spinal cord most common in the cervical region. Symptoms begin in second and third decade, usually slowly progressive. Sensory and then motor dysfunction.



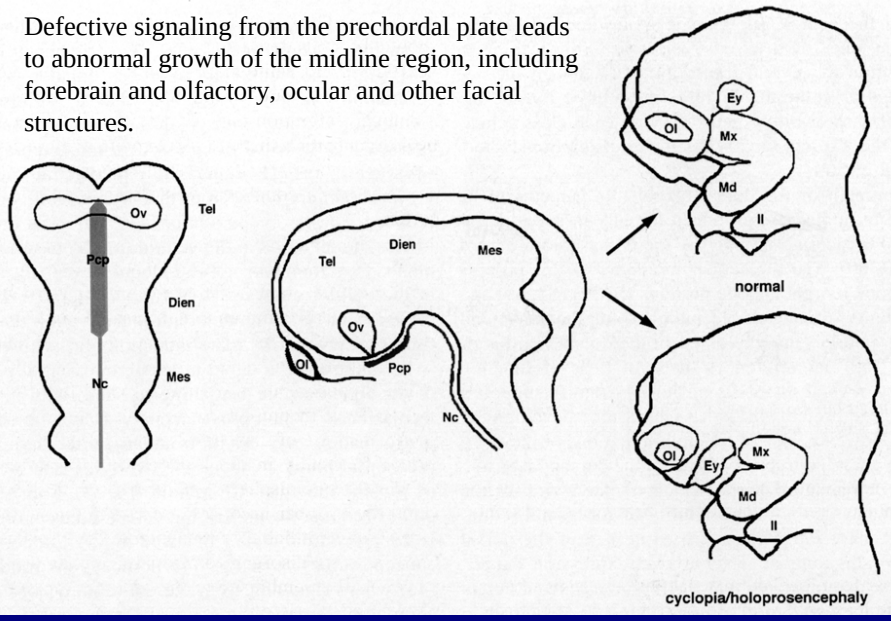


Holoprosencephaly

- Incidence = 0.5/10,000 live births; 40/10,000 abortuses
- Major brain malformation, including:
  - single telencephalic vesicle
    - (alobar, semilobar and lobar forms)
  - continuity of the cerebral hemisphere across the midline
  - absent olfactory bulbs/tracts
- Craniofacial abnormalities:
  - midline facial clefts, cyclopia, nasal anomalies
- Genetic/Environmental Factors involved include:
  - Maternal DM and infections (toxoplasmosis, CMV, syphilis)
  - trisomy 13
  - defects in sonic hedgehog signaling
- Pathogenetic studies demonstrate a failure in forebrain induction from the prechordal plate

Holoprosencephaly: A defect in brain patterning

Defective signaling from the prechordal plate leads to abnormal growth of the midline region, including forebrain and olfactory, ocular and other facial structures.



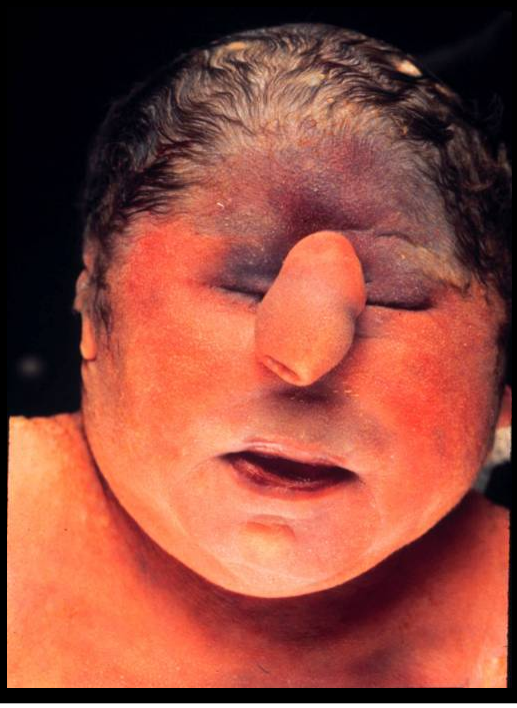
Facial Anomalies in Holoprosencephaly

Eyes: Hypotelorisim to cyclopia
Microphthalmia
Narrowed eyelids

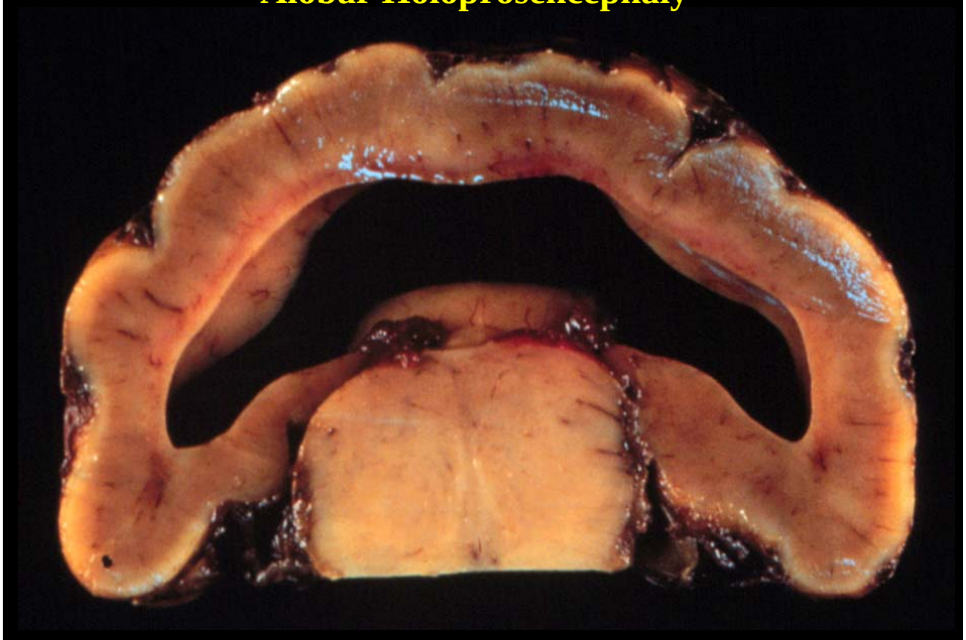
Nose: Proboscis to flattened

Uni- or bilateral cleft lip

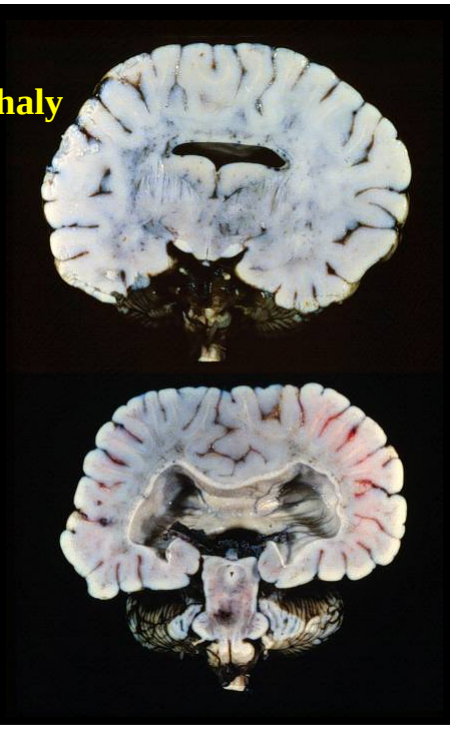
Cleft palate



Alobar Holoprosencephaly



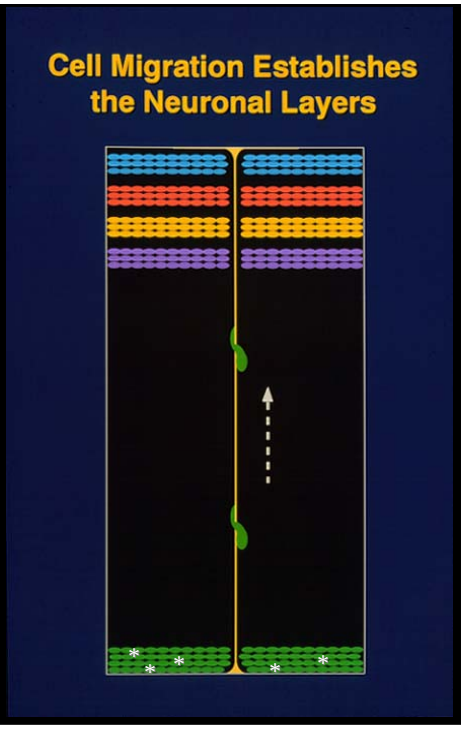
Lobar Holoprosencephaly



Neuronal migration disorders (Cortical malformation disorders)

May be caused by abnormalities in:

- Precursor cell proliferation
- Initiation of migration away from these zones
- Migration process to final destination
- Termination of migration/layer identity



Types of Neuronal Migration Disorders

Lissencephaly (agyria-pachgyria spectrum) **
- Miller-Dieker syndrome
- Isolated lissencephaly sequence

Cobblestone Lissencephaly
- Walker-Warburg syndrome
- Muscle-eye-brain disease
- Fukuyama congenital muscular dystrophy

Polymicrogyria **
- Associated with disruptive/destructive lesions, in utero infections (e.g. CMV), other;
- Bilateral, partial (frontal, perisylvian, parietal or posterior)

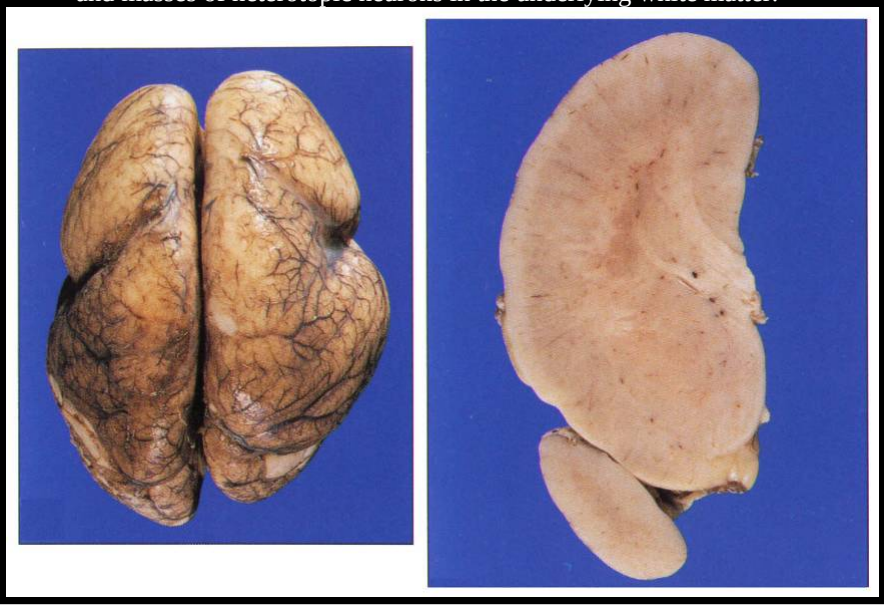
Diffuse Heterotopia
- Leptomeningeal heterotopia
- Periventricular nodular heterotopia (unilateral or bilateral)
- Subcortical band heterotopia ("double cortex")

Focal Heterotopia **
- Subcortical **
- Subependymal

** = most common

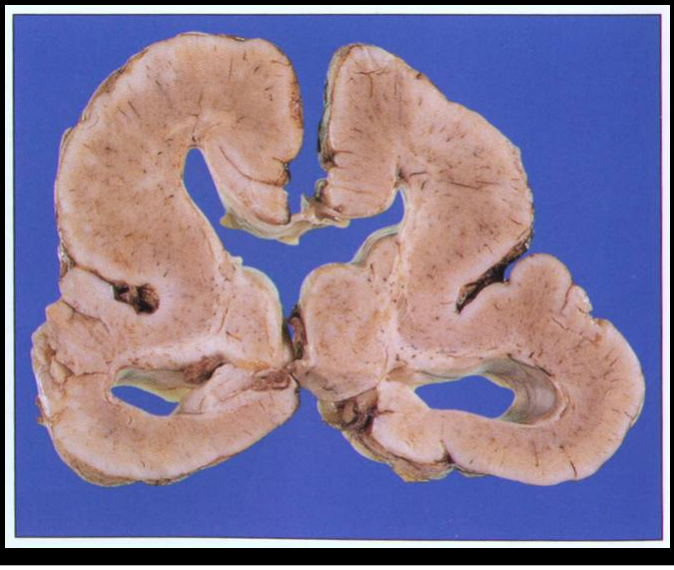
Lissencephaly

An example of agyric cortex. The cut section reveals a very thick cortex and masses of heterotopic neurons in the underlying white matter.



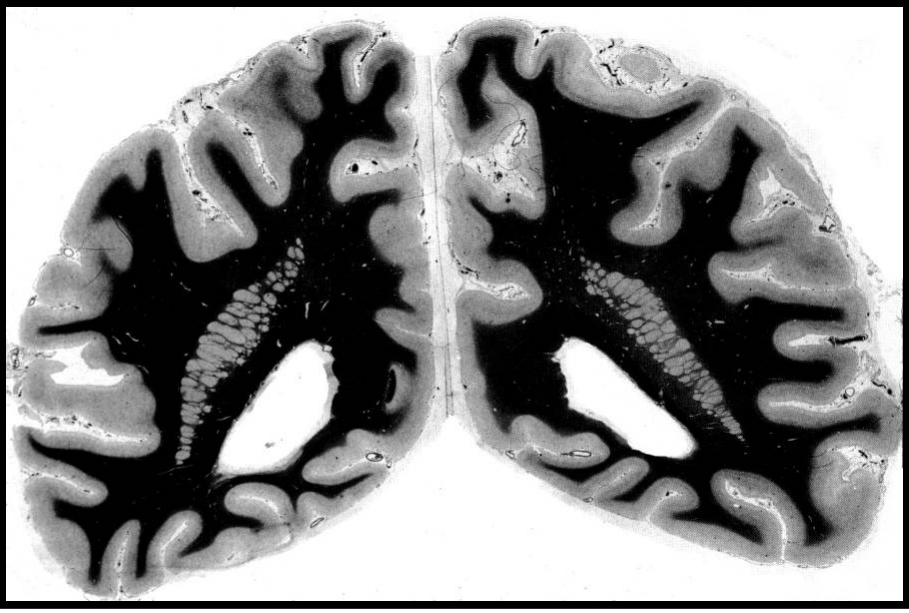
Lissencephaly

Predominantly agyric cortex but also a few large gyri (macrogyria). Most lissencephalies have a variable combination of agyria-macrogyria and represent a spectrum of disorders with varying clinical severity.



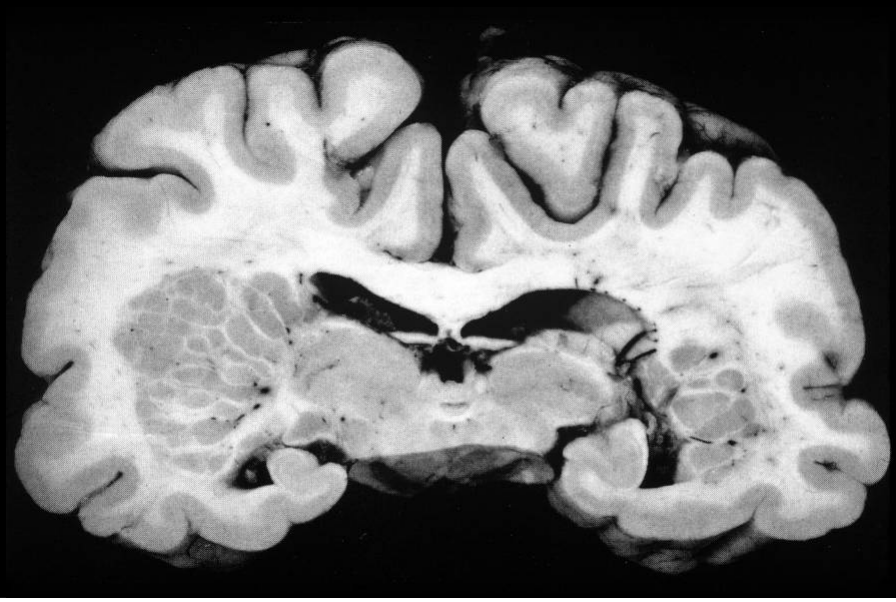
Laminar Hetertopia

Bilateral masses of heteropic neurons in white matter underly an apparently normal cerebral al cortex. When this is diffuse throughout the cerebrum it is called “Double cortex” syndrome.



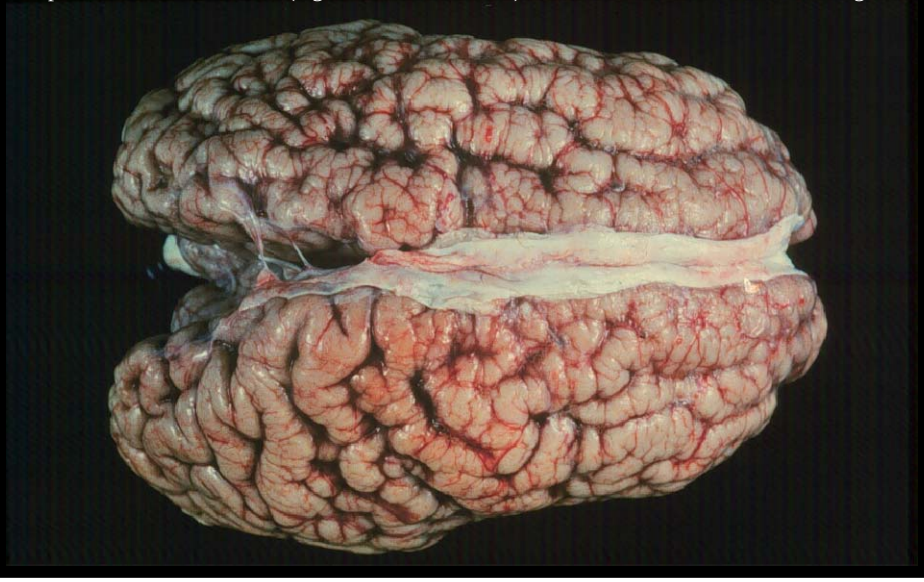
Nodular Hetertopia

Large masses of heterotopic neurons in white matter near the cerebral ventricle. May be bilateral or unilateral.



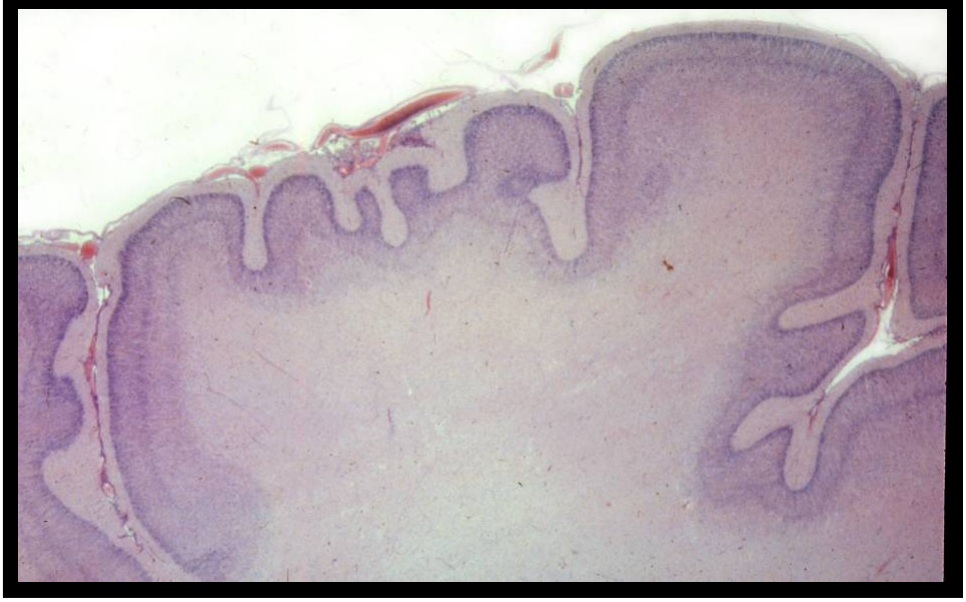
Polymicrogyria

Gyri that are too small and too numerous give a very cobbled appearance to the surface of the brain. This condition is most often sporadic, may be focal, and is associated with *in utero* disruptive/destructive lesions (e.g. infarcts, infections). Rare inherited disorders are recognized.



Polymicrogyria

Numerous small gyri with fusion of molecular layer between adjacent microgyri (absence of vascular space along length of many gyri).



Developmental Neuropathology

PERINATAL

Aquired due to hypoxia, ischemia, trauma

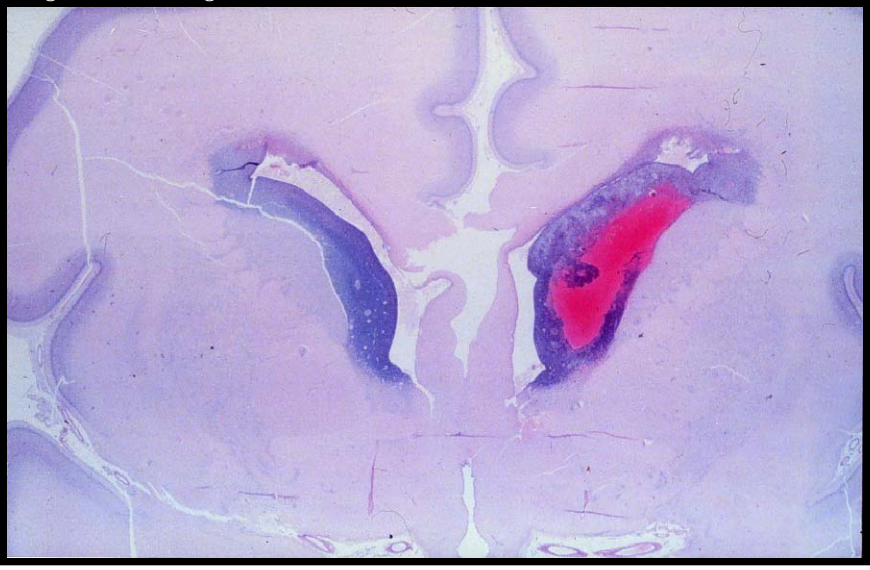
Germinal matrix hemorrhage

Periventricular leukomalacia

Infarcts (arterial territories or watershed infarcts in hypotension)

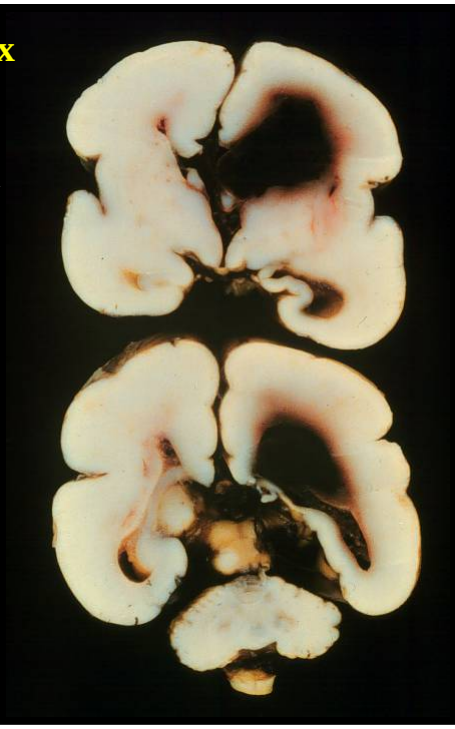
Germinal matrix hemorrhage

Hemorrhage limited to germinal matrix, here overlying the caudate nucleus. These lesions are seen in premature infants born before ~32-33 weeks EGA. Thin-walled vessels in this region are prone to rupture in association with hypoxia and poor cerebral blood flow autoregulation at this age.



Germinal matrix hemorrhage

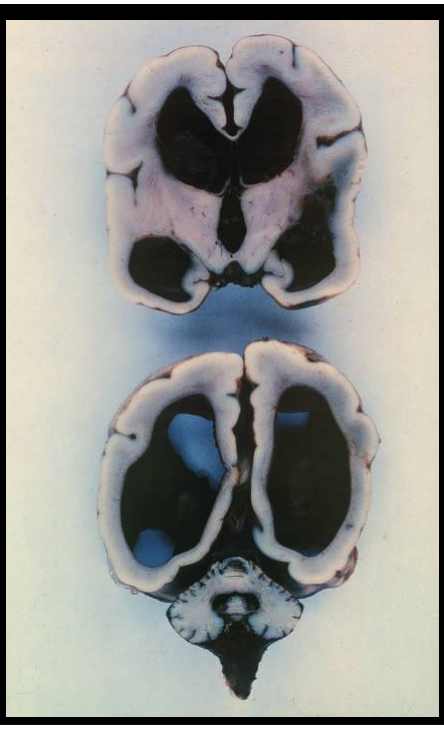
Large hemorrhage has extended into the adjacent brain.



Germinal matrix hemorrhage

Marked ventricular dilatation due to a germinal matrix hemorrhage that erupted into the ventricular system, causing an acute hydrocephalus.

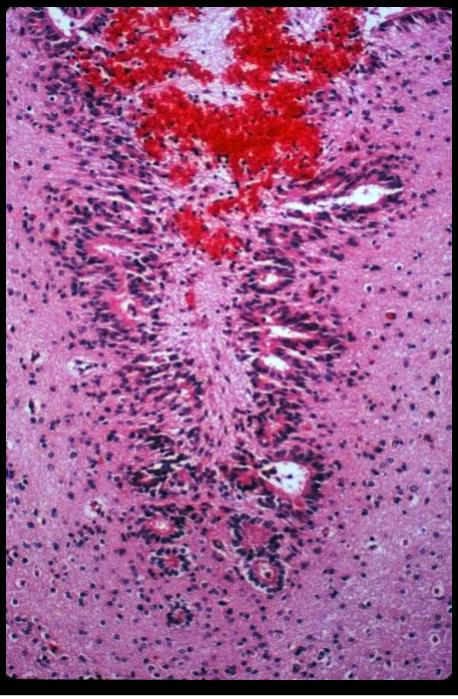
Blood around brainstem and cerebellum follows CSF flow.



Germinal matrix hemorrhage

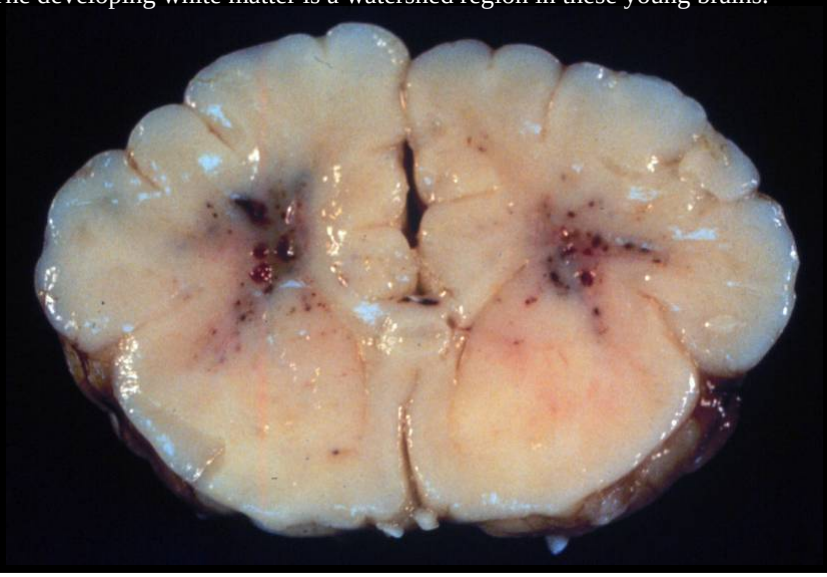
Sequelae of hemorrhage may include a non-communicating hydrocephalus due to occlusion of the cerebral aqueduct from breakdown and organization of blood products.

May also develop a communicating hydrocephalus due to organization of blood products in the subarachnoid space.



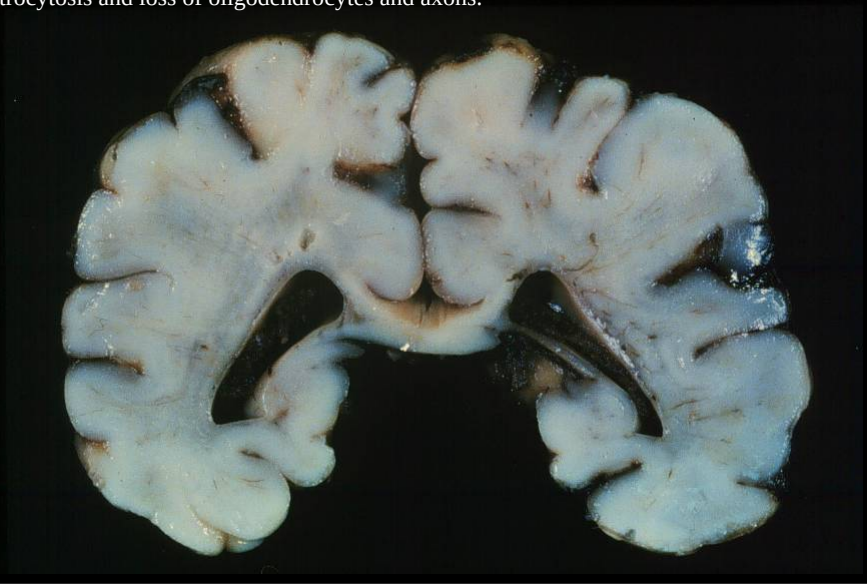
Periventricular Leukomalacia

Bilateral damage to white matter during periods of hypotension in premature and perinatal brain. Vascular congestion is present in the acute stage of the lesion. The developing white matter is a watershed region in these young brains.



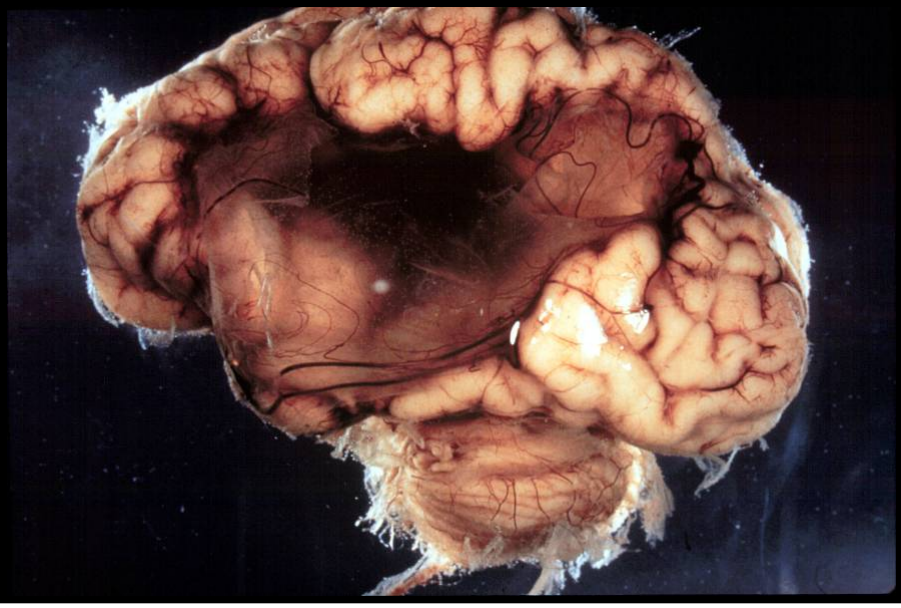
Periventricular Leukomalacia

Chalky white, cystic cavities in the white matter next to the ventricle are residua of prior ischemic lesions. Histologically, there is actually widespread damage to white matter with astrocytosis and loss of oligodendrocytes and axons.



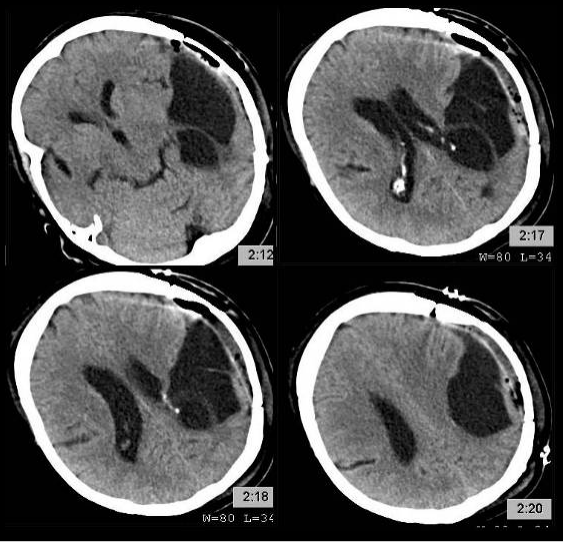
Porencephalic cyst

Large destructive cerebral lesion in territory of MCA resulting in communication between the cerebral ventricle and subarachnoid space. Often see polymicrogyria in adjacent cortex.



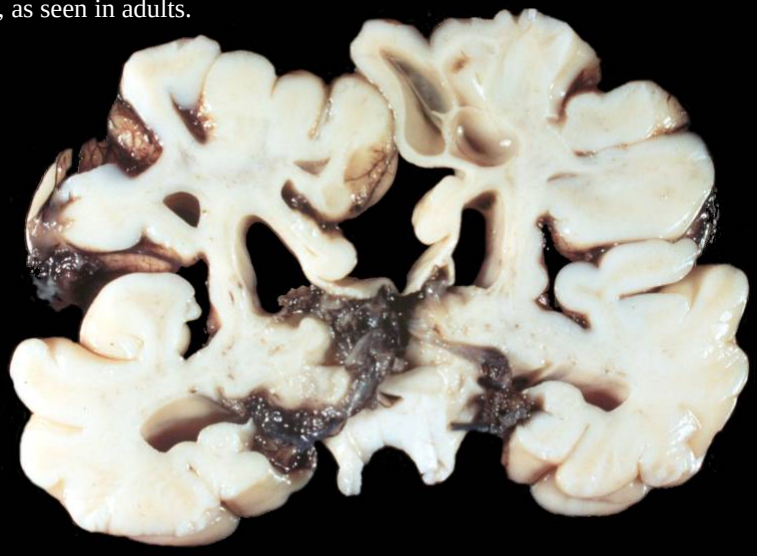
Porencephalic cyst

A 56 year old female with a history of breast carcinoma tripped and fell, sustained facial fractures and developed a subdural hematoma. This large porencephalic cyst was an incidental finding and related to known history of birth trauma. This is an unusual clinical history but demonstrates the plasticity of immature brain which may compensate for the defect.

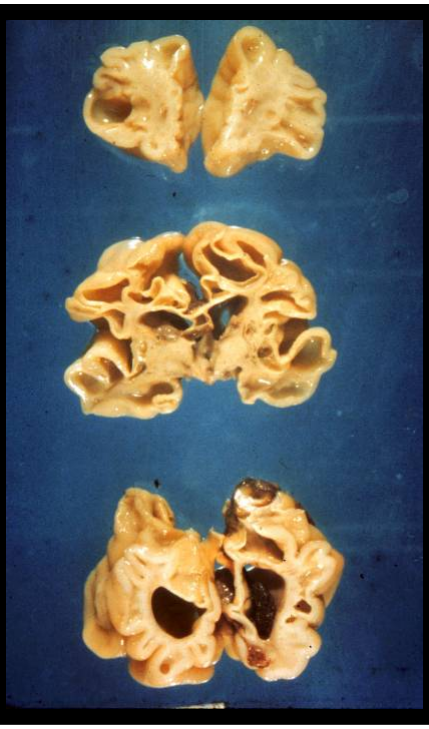


Multicystic encephalopathy

Perinatal, cortically based ischemic lesions. Cystic cavitation and glial response in brain, as seen in adults.



Multicystic encephalopathy



Neurocutaneous Syndromes (Phakomatoses)

Cellular proliferations (hyperplastic or neoplastic) which occur in association with malformations

Affect the nervous system and skin

Neurofibromatosis type I	**autosomal dominant**
Neurofibromatosis type II	**autosomal dominant**
Tuberous Sclerosis	**autosomal dominant**
Sturge-Weber syndrome	**?**

Von Recklinghausen Neurofibromatosis

First described in 1882. Most commonly known form is Neurofibromatosis type I (NFI) with several variant forms having different clinical features (NF2-NFVII).

Characteristics of NFI:

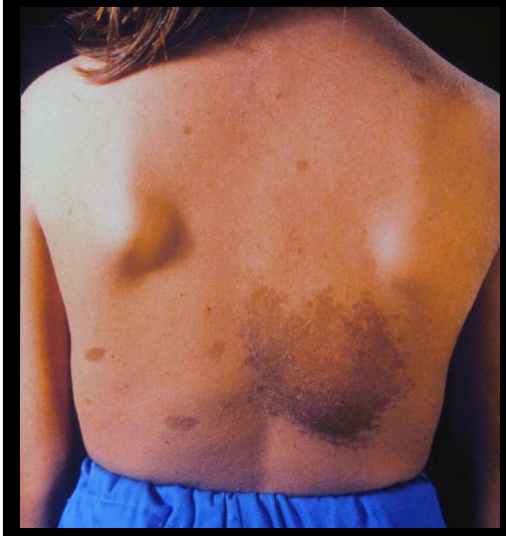
1) Autosomal dominant inheritance with variable expressivity and high penetrance. Prevalence of 1 in 2500 - 3000.

2) 50% of patients have an affected family member; the remaining represent new mutations.

3) Common lesions: Café-au-lait spots (>6,>0.5 cm), 90% of patients
Neurofibromas (cutaneous, deep, plexiform)
Pigmented iris hamartomas (Lisch nodules)
Axillary or groin freckling
Skeletal abnormalities (e.g. scoliosis)
Learning disorders
Increased risk of malignancy/other tumors

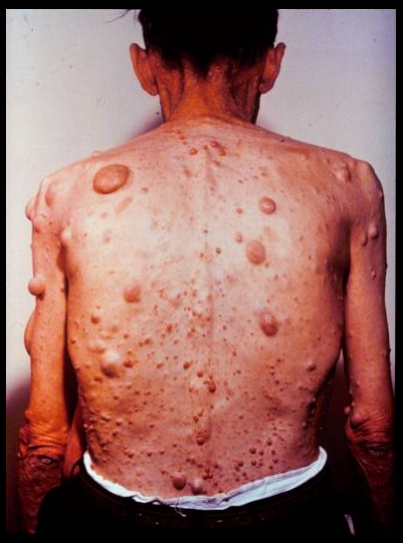
Café-au-lait spots

Multiplicity and size of lesions are important for diagnosis of neurofibromatosis.



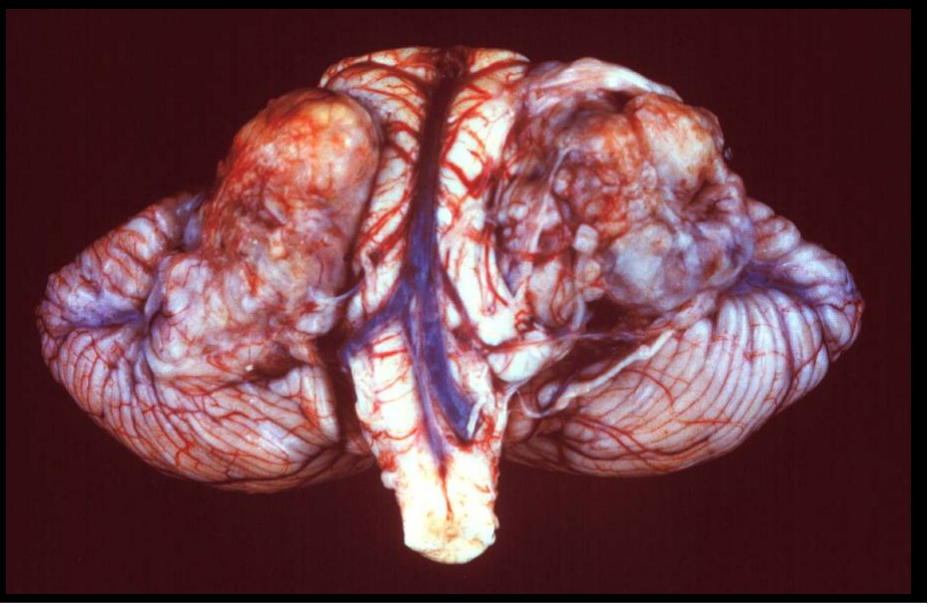
Neurofibromas

A tumor of peripheral nerve. Usually benign but may become malignant, particularly those in deeper nerves and plexuses. Plexiform neurofibromas are pathognomonic for NFI.



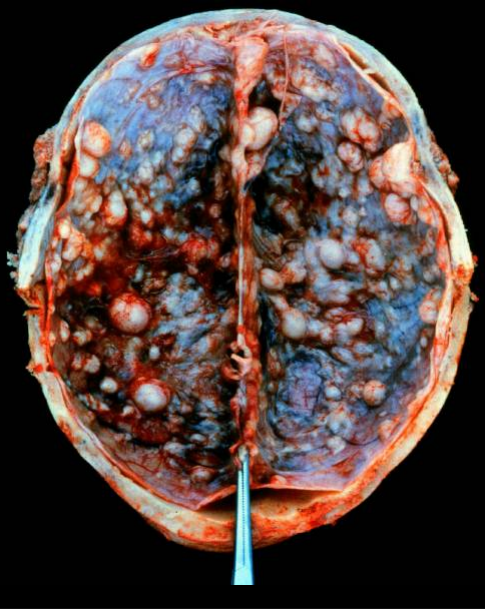
NF-type 2: Bilateral acoustic schwannomas

Schwannomas are a benign tumor of peripheral nerve and are most often sporadic. When present bilaterally on both VIIIth nerves, this is pathognomonic for NF-type 2.



Numerous meningiomas (a tumor of arachnoid cells) lining the arachnoid under the skull in this patient with NF-2.

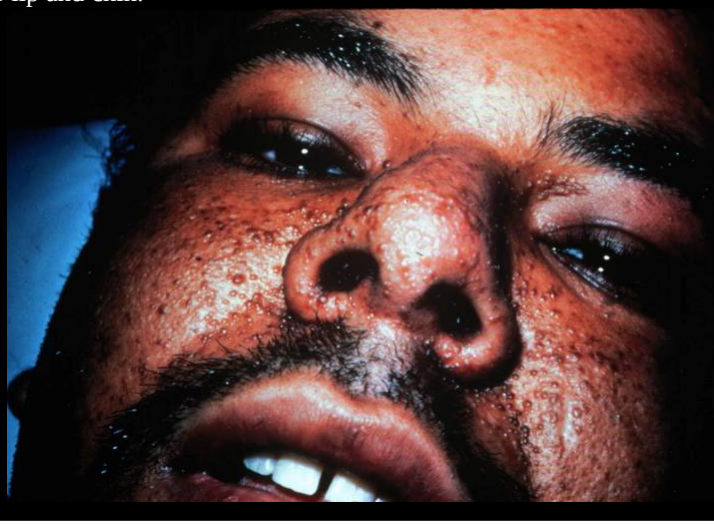
Both NF-1 and NF-2 patients also develop primary CNS gliomas with increased frequency.



Tuberous sclerosis

Variable clinical presentations but may present in the first year of life with seizures. Mental retardation and behavioral problems also common.

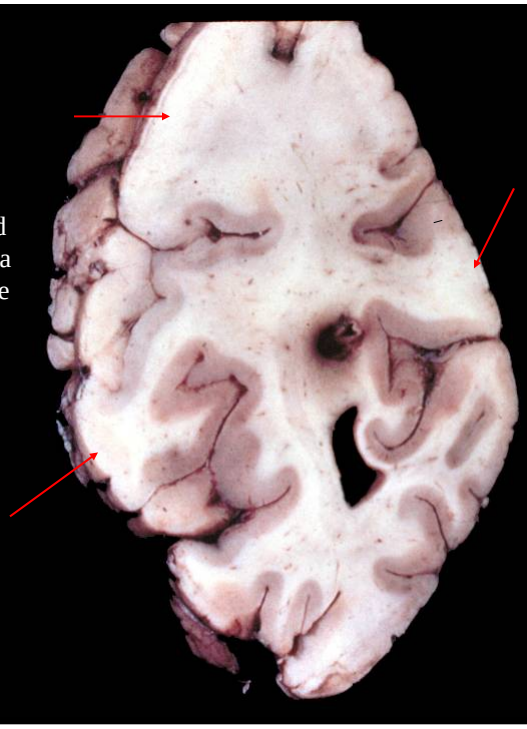
Facial angiofibromas (adenoma sebaceum) are a common skin manifestion and appear between 2 and 5 years of age. Form a butterfly rash over the cheeks, nose, lower lip and chin.



Tuberous sclerosis

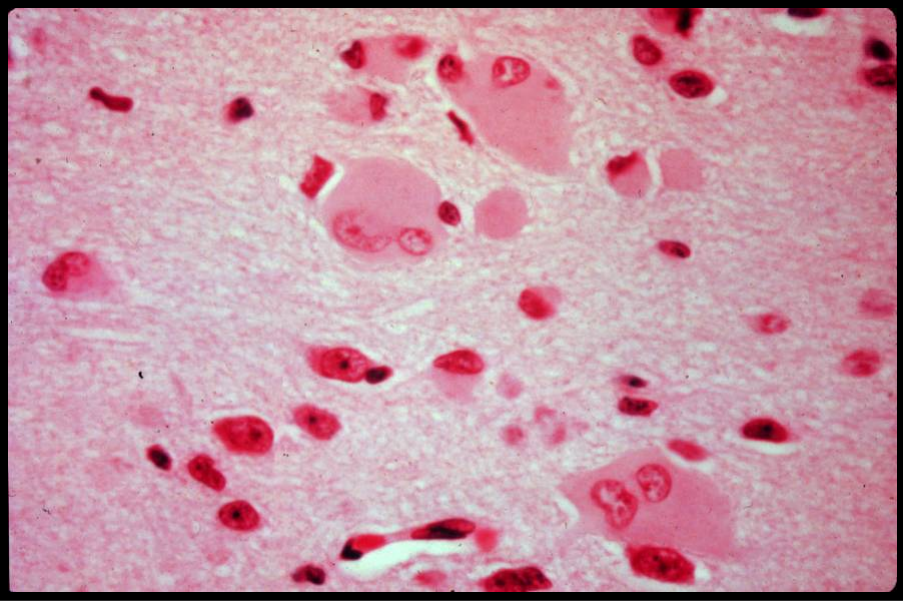
Cortical tubers

The tuber is a cortical malformation containing an abnormal mixture of neurons and glial cells. On cut surface it has a gritty and firm texture. These are commonly seizure foci these patients.



Tuberous sclerosis **Cortical tubers**

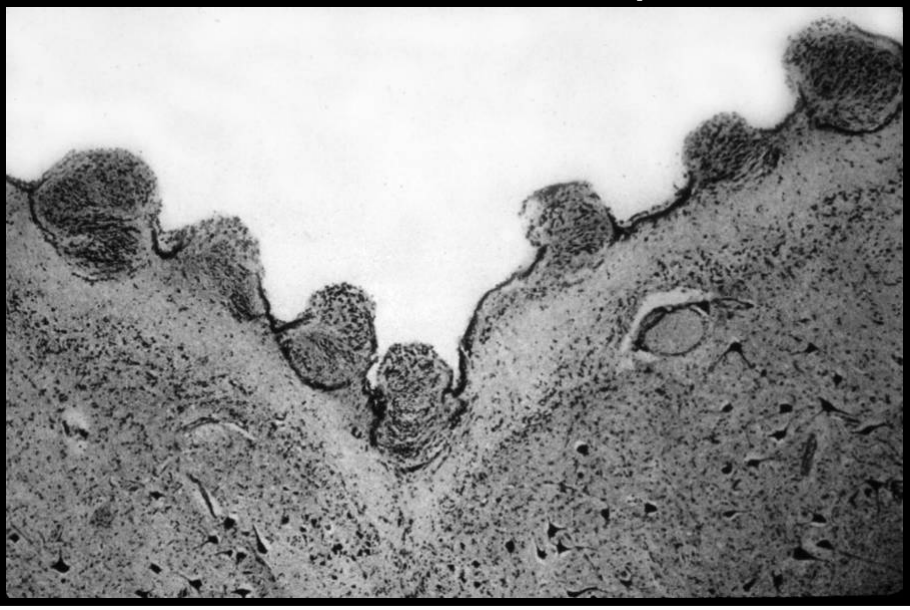
Bizzarre giant cells (have both neuronal and astrocytic features) admixed with neurons and astrocytes in a cortical tuber.



Tuberous sclerosis

Subependymal nodules ('candle gutterings')

Benign astrocytic proliferations beneath the ependyma, most commonly in the lateral ventricles but also in third & fourth ventricle and aqueduct. Often calcified.



Sturge-Weber syndrome

- Large 'port-wine stain' [naevus] in the trigeminal territory
- Ocular angioma, glaucoma
- Leptomeningeal angiomatosis and cerebral atrophy ipsilateral to side of naevus
- Symptoms such as hemiparesis, hemiplegia, epilepsy and mental retardation generally begin within the first year of life or early childhood
- Sporadic disorder, pathogenesis is poorly understood.