CENTRAL NERVOUS SYSTEM DEVELOPMENT

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Neurulation

- The process of formation of the hollow neural tube by folding of the epithelial neural plate.
- Begins with local elongation of the ectoderm cells in a midline zone of the embryonic disc (notochord) and their re-organization into the neural plate by day 22 (endoderm).
- This is followed by reshaping and bending of the neural plate into a neural groove, which closes to form a neural tube from the mid portion to its cranial and caudal ends.
- A continuous surface ectoderm forms dorsal to the tube.

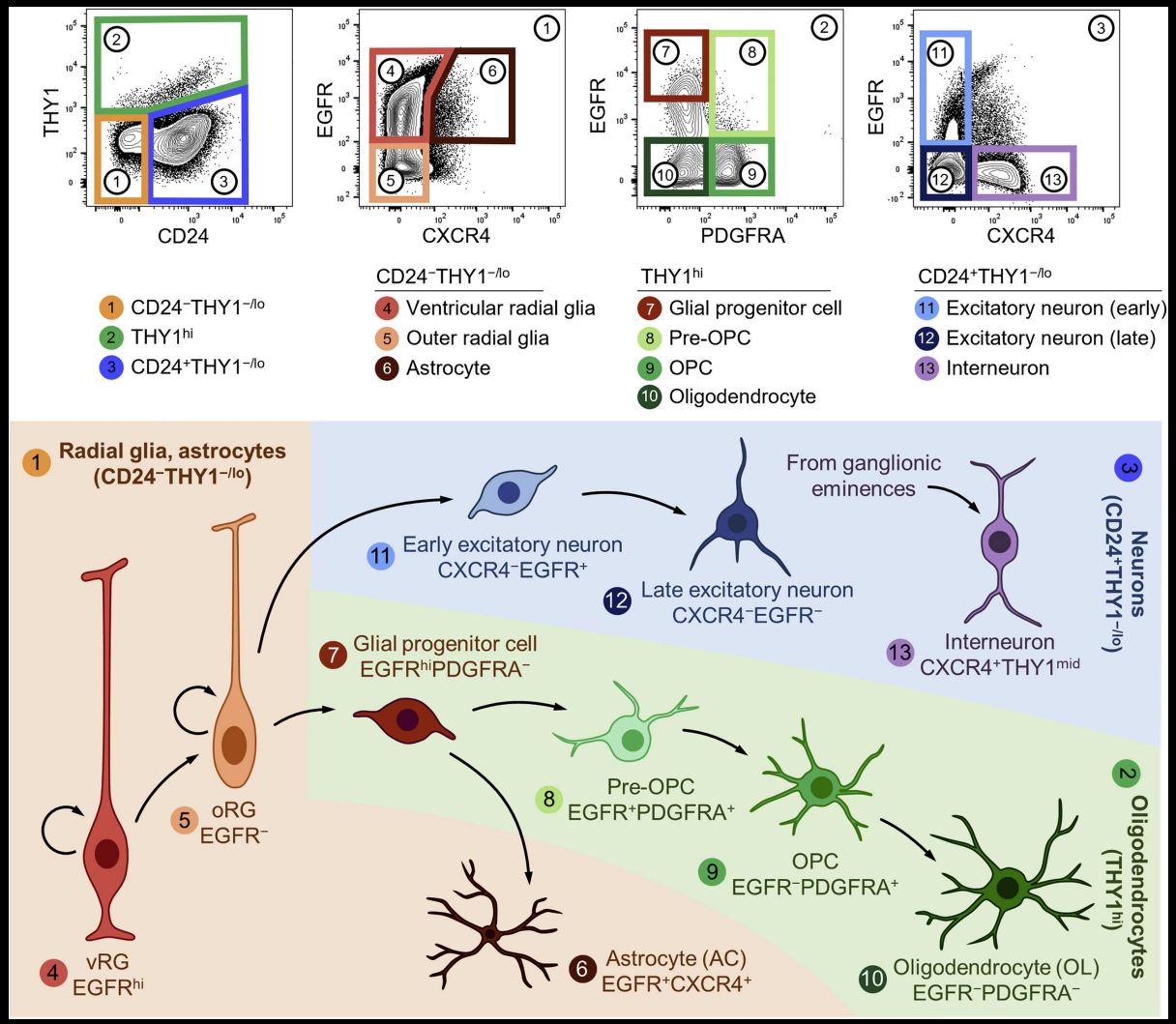
Neurulation

- In the developing cerebral cortex, radial glia serve as neural stem cells that self-renew and give rise to progressively more lineage-restricted progenitors.
- Ventricular radial glia that reside in the ventricular zone maintain both apical and basal processes
- Outer radial glia reside in the outer subventricular zone and maintain only their basal processes
- Neural progenitor cells are CD133+CD24-THY1-
- Ventral glial cells are CD133+CD24-
- EFGR+ ventricular zone radial glial cells
- EFGR- outer ventral zone radial glial cells

Neurulation

- EFGR+CXCR4+ cells astrocyte lineage
- Express PAX3
- Are GFAP+
- EFGR- outer ventral zone radial glial cells
- EFGR+PDGFRA+ oligodendrocyte precursors
- EGFR-PDGFRA+ early oligodendrocytes
- EGFR-PDGFRA- glial progenitor cell
- EGFR-PDGFRA- mature oligodendrocytes
- Neuronal lineage cells are CD133+CD24+THY1-
- CXCR4+ cells interneurons
- CXCR4- cells excitatory neurons

Figure 7



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Neurulation

- The brain's divisions do not mature simultaneously but at intervals (heterochronous maturation).
- Primary neurulation occurs during weeks 3 and 4 of gestation leading to development of the brain and spinal cord.
- Secondary neurulation occurs during weeks 5 and 6, with formation of the lower sacral and coccygeal cord.
- SHH gradients control neural development. Originate from notochord
- PAX 6 involved in neurogenesis

Embryonic development

- **Neural tissue stratified. Migration occurs in waves.**
- **Wave 1: Neuro-epithelial cells near the ventricle (ventricular layer) continually divide and give rise to neuroblasts.**
- **Cell bodies and astrocytes are found in middle layer.**
- **Marginal (sub-pial) layer contains nerve fibers and oligodendrocytes.**
- **Wave 2: Macroglioblasts will form most glia cells (microglia come from mesenchyme not ectoderm).**
- **Failure of migration leads to multiple cysts or smooth cerebral convolutions or even heterotopic tissue.**

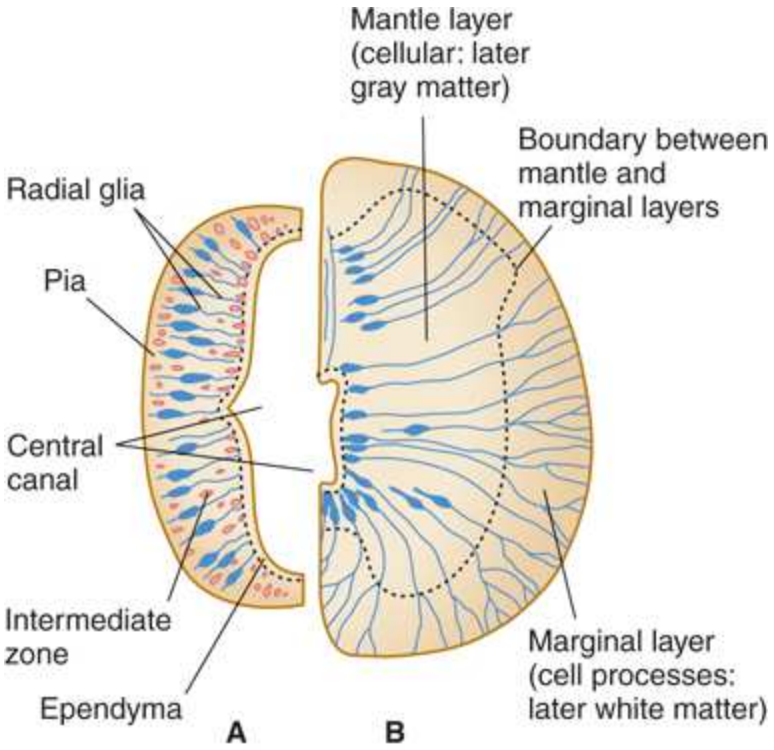
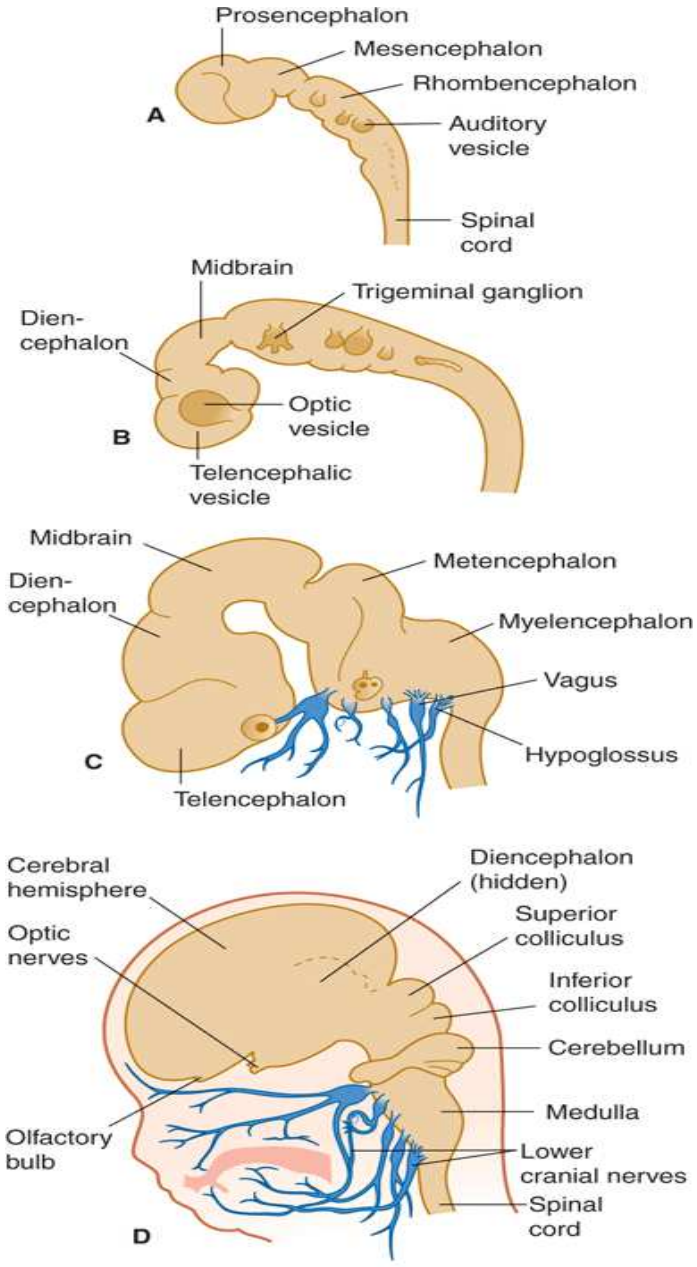


Fig. 2-1 Accessed 07/01/2010

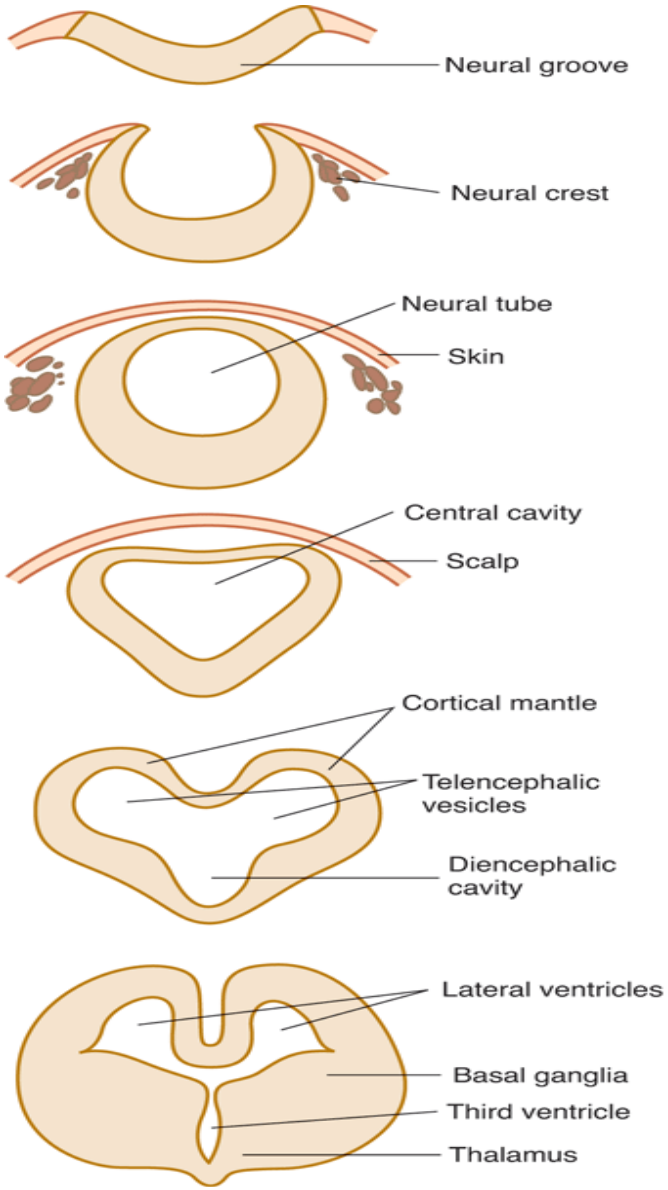
Embryonic development (overview)



A: 3½ weeks
B: 4½ weeks
C: 7 weeks
D: 11 weeks

Fig. 7-1 Accessed 07/01/2010

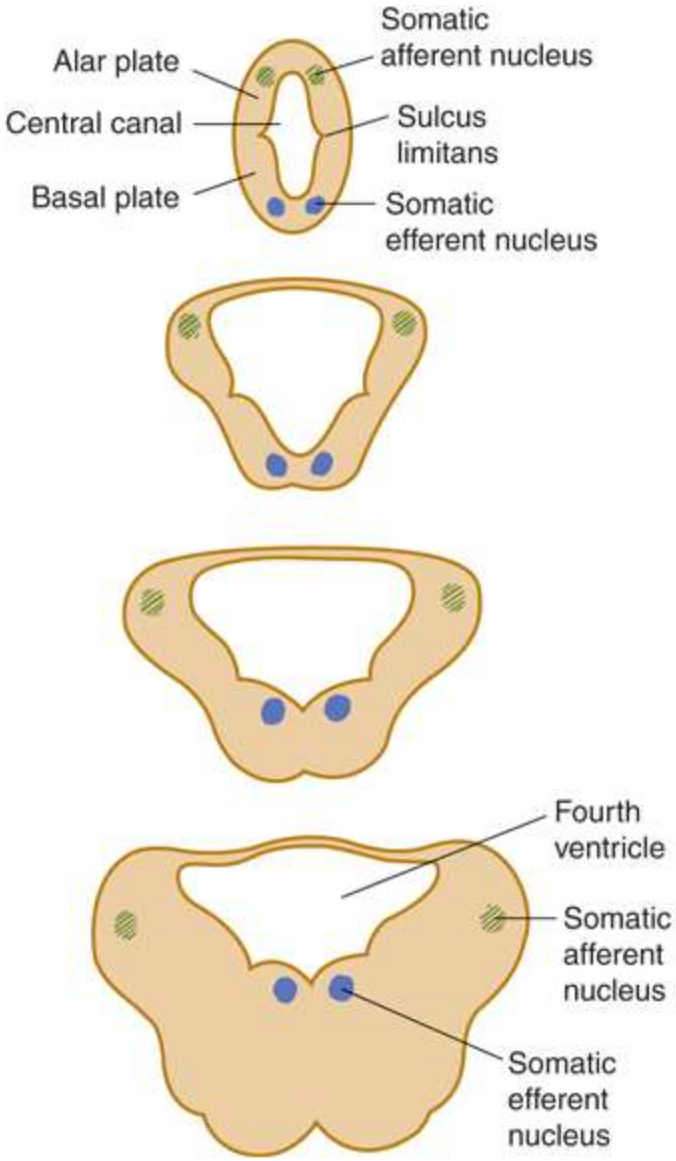
Embryonic development (overview)



Cross sections showing early development from neural groove to cerebrum.

Fig. 10-1 Accessed 07/01/2010

Embryonic development (overview)

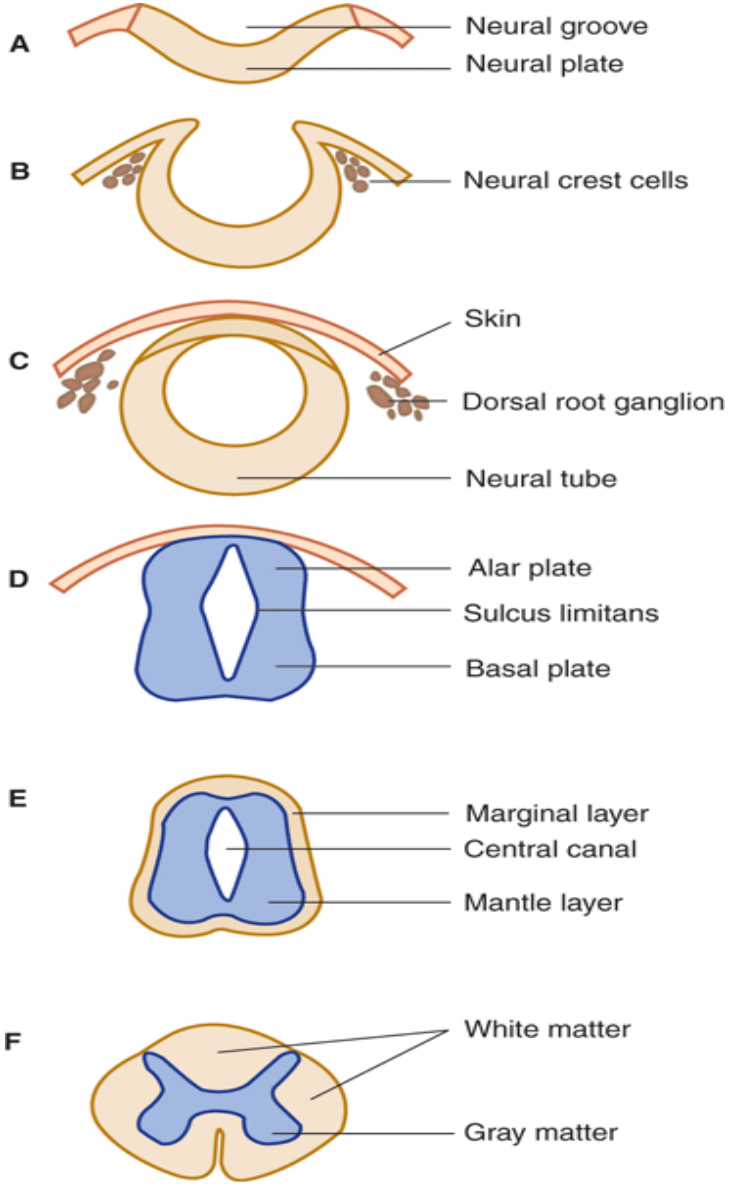


Source: Waxman SG: *Clinical Neuroanatomy, 26th Edition*: http://www.accessmedicine.com

A similar arrangement occurs in the brainstem. However in the upper medulla and pons, structures are shifted by the development of the fourth ventricle.

Fig. 7-2 Accessed 07/01/2010

Embryonic development (overview)



Source: Waxman SG: *Clinical Neuroanatomy, 26th Edition*: http://www.accessmedicine.com

Cross sections showing early development from neural groove to spinal cord.

Fig. 10-1 Accessed 07/01/2010

Developmental anomalies

- The pathogenesis and etiology of many central nervous system malformations is multifactorial.
- Neural tube defects account for the large majority of central nervous system malformations.
- The failure of the neural tube to close (by day 28) or opening after successful closure may lead to malformation of neural tissues, meninges, as well as overlying bone and soft tissue.

Neural tube defects

- The recurrence rate in future pregnancies is about 5%.
- Folate deficiency is a risk factor.
- Screen with alpha-fetoprotein levels (adjusted to estradiol levels) and ultrasound.

Neural tube defects

- Spina bifida
- Local regions of the spinal neural tube are unfused, or
- There is failure of formation of the vertebral neural arches,
- Most common in lumbosacral region
- Asymptomatic in spina bifida occulta.
- May see dimple or tuft of hair of skin overlying L5-S1.
- Bowel and bladder abnormalities, foot drop

Neural tube defects

- Meningocele (cystic mass containing meninges)
- Meningomyelocele (cystic mass containing meninges and spinal cord)
- Generally invovle the lumbosacral region
- Affected individuals have motor and sensory deficits in the lower extremities as well as disturbances of bowel and bladder control.
- Thin sac covering is poor barrier to prevention of infection

Meningomyelocele

http://en.atlaseclamc.org/images/__files/images/1388379148-680x400.jpg
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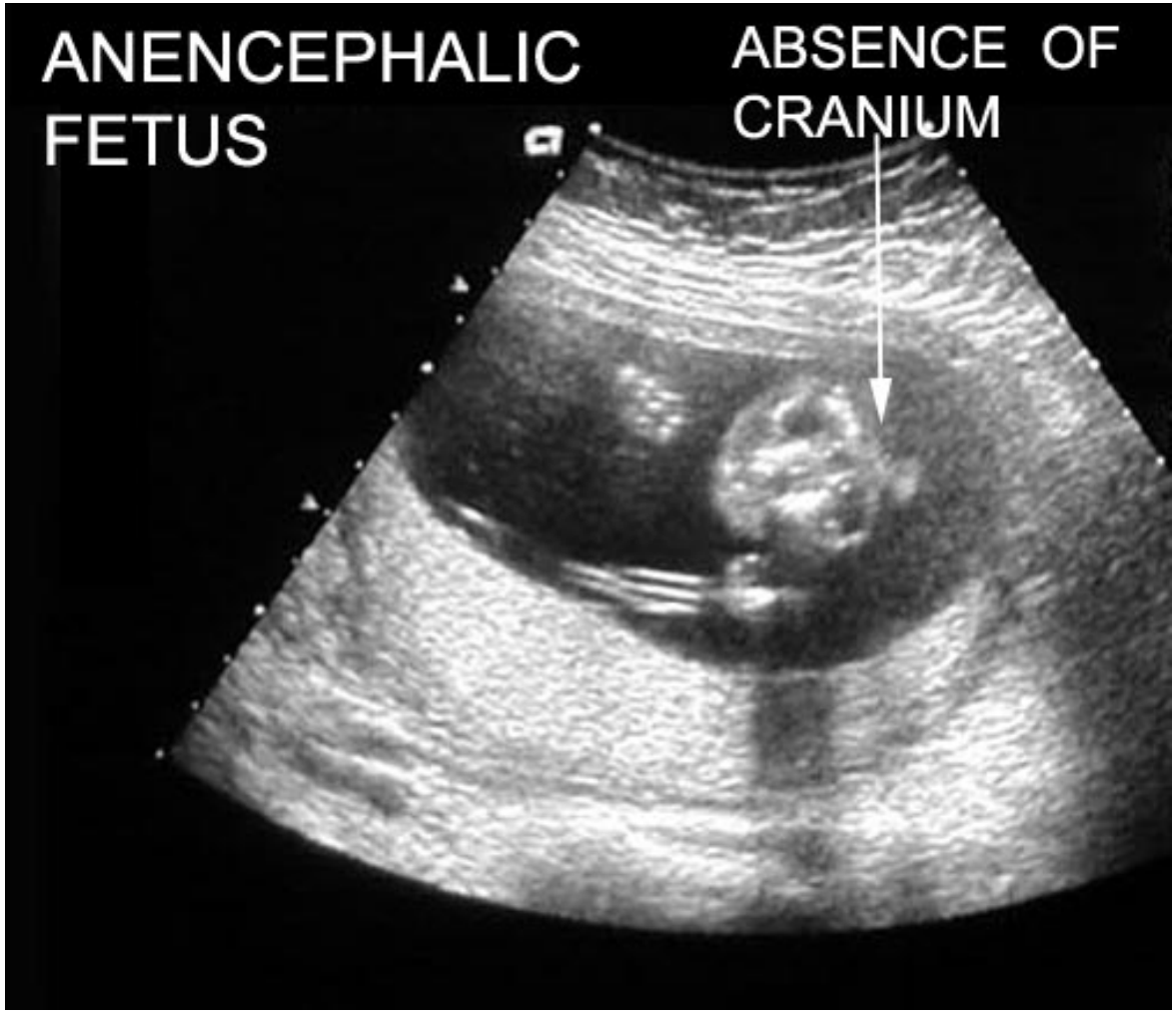
Neural tube defects

- Encephalocele refers to a diverticulum of malformed brain tissue extending through a defect in the cranium.
- It most often occurs in the posterior fossa, although comparable extensions of brain occur through the cribriform plate in the anterior fossa.

Failure of neurulation

- Craniorachischisis totalis
- The entire neural tube is unfused dorsally in the midline
- Cranioschisis or Anencephaly
- The neural tube is fused dorsally to form the spinal cord but is not fused dorsally in the brain
- Area cerebrovasculosa alone remains
- Flattened remnant of disorganized brain tissue with admixed ependyma, choroid plexus, and meningothelial cells. The posterior fossa structures may be spared, depending on the extent of the skull deficit
- Complete absence of brain

Anencephaly



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Accessed 11/26/2019

Anencephaly

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Forebrain abnormalities

- Abnormalities in the generation and migration of neurons result in malformations of the forebrain that may be focal or involve entire structures.
- The pool of proliferating precursor cells in the developing brain lies adjacent to the ventricular system.
- Overall neuronal number is determined by the fraction of proliferating cells that undergo transition into migrating cells with each cell cycle.

Forebrain abnormalities

- The migration of neurons from the germinal matrix zone to the cerebral cortex follows two paths:
- (1) a radial migration for neuronal progenitor cells destined to become excitatory neurons
- (2) a tangential migration course for those which will become inhibitory interneurons.
- For radial migration, a secreted protein (reelin) signals to migrating neuroblasts through a surface receptor.

Forebrain abnormalities

- Megalocephaly
- Microcephaly
- A reduction in the number of neurons that reach the neocortex leads to a simplification of the gyral folding
- Fetal-alcohol syndrome
- HIV-1 infection in utero

Forebrain abnormalities

- Lissencephaly
- A reduction in the number of gyri
- In the extreme case may show no gyral pattern *(*agyria*)*
- Type 1 (smooth surface) is associated with mutations that disrupt the signaling for migration and the cytoskeletal “motor” proteins that drive migration of neuroblasts.
- Type 2 (cobblestone surface) is associated with genetic alterations that disrupt the “stop signal” for migration.

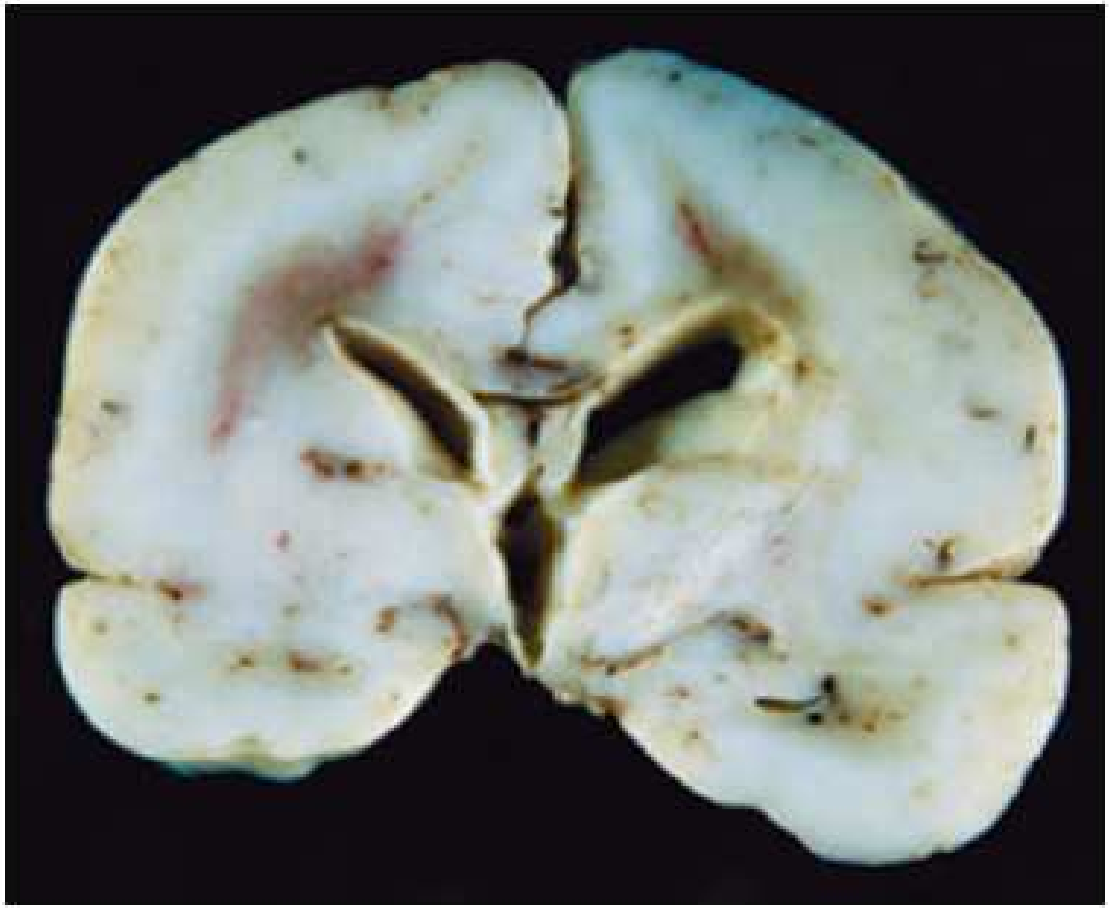


Figure 28-5 Lissencephaly. The absence of cortical gyri defines this abnormality, seen here in the brain from a full-term infant.

Forebrain abnormalities

- Polymicrogyria is characterized by small, unusually numerous, irregularly formed cerebral convolutions.
- The gray matter is composed of four layers (or fewer), with entrapment of apparent meningeal tissue at points of fusion that would otherwise be the cortical surface.
- Polymicrogyria can be induced by localized tissue injury toward the end of neuronal migration.

Forebrain abnormalities

- Neuronal heterotopia
- Frequently found along ventricular surface (failure of migration)
- FLNA mutation (filamin, an actin binding protein) at Xq28
- Lethal for male
- DCX mutation (doublecortin, a microtubule protein associated with neurogesis) at Xq23
- Lissencephaly in male
- Bands of subcortical nodules in females

Forebrain abnormalities

- Holoprosencephaly
- A spectrum of malformations characterized by incomplete separation of the cerebral hemispheres across the midline.
- Severe forms manifest midline facial abnormalities, including cyclopia
- Less severe variants show absence of the olfactory cranial nerves and related structures (arrhinencephaly)
- May have proboscis
- Trisomy 13
- Abnormality of SHH pathway
- Incompatible with life

Forebrain abnormalities

- Agenesis of the corpus callosum
- "Bat-wing" deformity on x-ray (misshapen lateral ventricle)

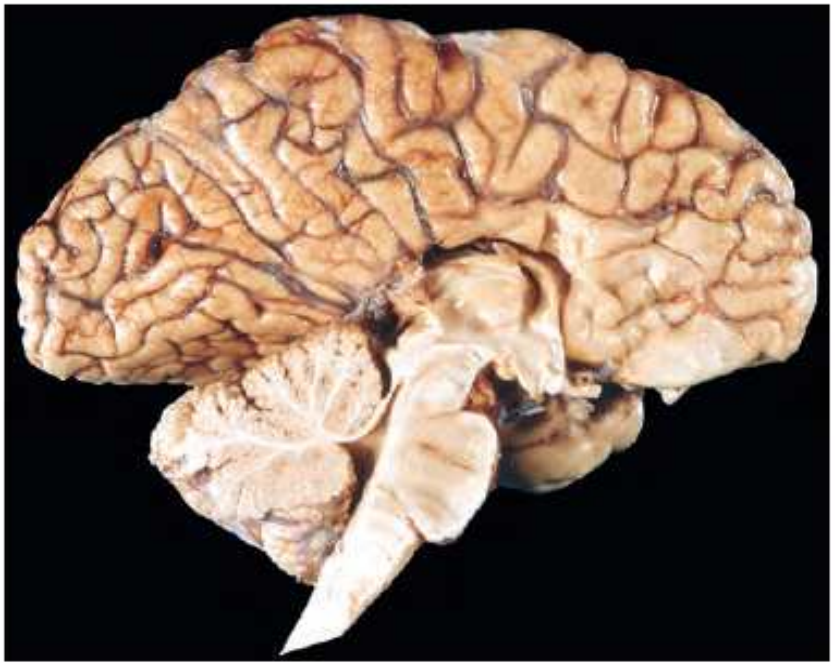


Figure 28-6 Agenesis of the corpus callosum. The midsagittal view of the left hemisphere shows the lack of a corpus callosum and cingulate gyrus above the third ventricle.

Arnold-Chiari malformation

- Underdevelopment of the occiput.
- Portions of the spinal cord may be visible through a skull defect
- Infant may present with difficulty nursing
- Other neurologic deficits related to areas of brainstem affected
- Usually there is obstruction to passage of cerebrospinal fluid at the level of the foramen magnum.
- Hydrocephalus a likely development

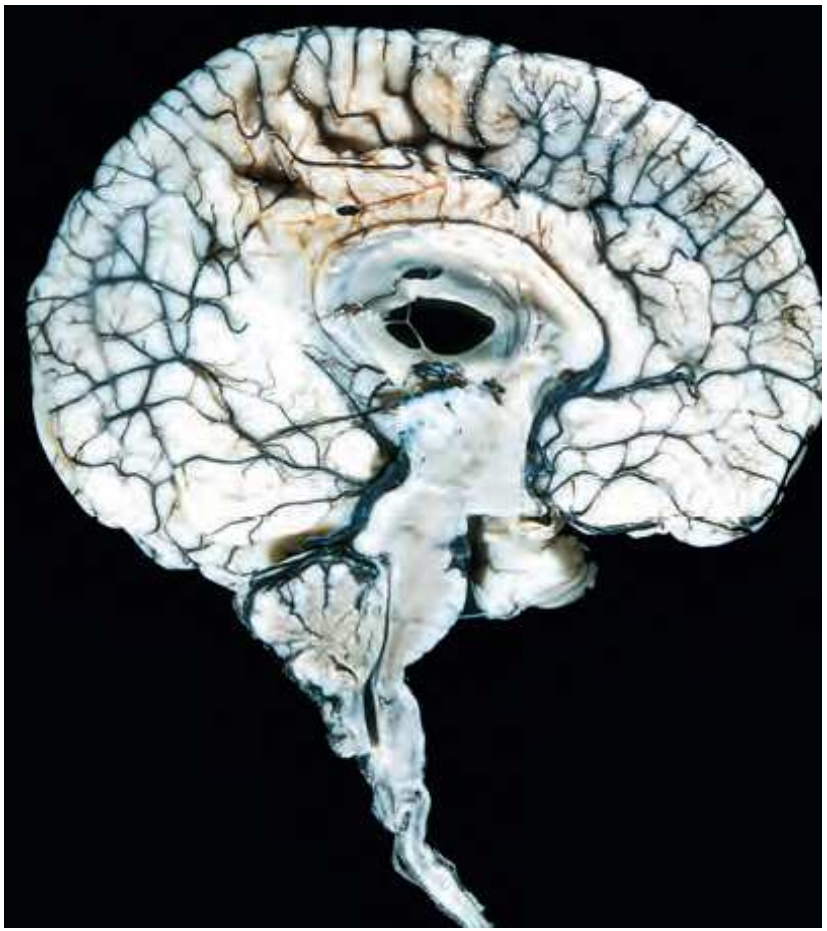
Arnold-Chiari malformation

- Type 1
- Unilateral or bilateral cerebellar tonsillar herniation without displacement of medulla
- Most common
- Presents in adolescence
- May be silent, however
- Increased intracranial pressure may lead to syringomyelia in the cervical cord.
- Type 2
- Caudal displacement of the medulla
- Usually associated with meningomyelocele.
- Presents in infancy

Arnold-Chiari malformation

- Type 3
- An encephalocele and breaking of the quadrigeminal plate
- Presents in infancy
- Type 4
- Undeveloped cerebellum

Arnold-Chiari malformation



Frosch, MP, Anthony, DC, De Girolami, U, “The Central Nervous System,” in Kumar, V, Abbas, AK, Aster, JC, (eds), Robbins and Cotran Pathologic Basis of Disease (9th ed.), Elsevier. Philadelphia. (2015) Fig. 28-7 Accessed 10/25/2019

Dandy-Walker malformation

- Presents shortly after birth in 80% of cases
- Macrocephaly (due to hydrocephalus)
- Intellectual disability
- Slow neurological development of motor skills
- May develop spastic paraplegia
- If presents as child or adult, headaches, an unsteady walking gait, paralysis of facial muscles (facial palsy) are noted
- Usually trisomy 13

Dandy-Walker malformation

- 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

Other posterior fossa malformations

- Joubert syndrome
- Hypoplasia of the cerebellar vermis with apparent elongation of the superior cerebellar peduncles and an altered shape of the brainstem
- “Molar tooth sign” on imaging

Syringomyelia

- 3rd-4th decade
- Fluid filled cavity (syrinx) within cervical spinal cord or bulbar area
- Obstruction of 4th ventricle (may follow trauma)
- Cavity expands leading to pressure degeneration of spinal tracts.
- Disrupt crossed lateral spinothalamic tracts
- Loss of pain and temperature sense in the hands
- Tactile sense preserved
- Destruction of anterior horn cells
- Atrophy of intrinsic muscles of hands

Developmental anomalies

- Platybasia.
- A flattening of the skull base.
- Asymptomatic.
- Occipitalization of C1.
- Synostosis of C1 with the occiput.
- May present with medullary dysfunction and requires surgical intervention.

Developmental anomalies

- Basilar impression syndrome.
- Underdevelopment of the occipital bone.
- Cervical spine relatively elongated.
- Presents with occipito-cervical pain and reduced neck flexibility.
- May progress and require surgical intervention.

Developmental anomalies

- Kippel-Feil syndrome.
- Fused cervical vertebrae.
- Short neck, high shoulders, abnormal posture.
- May have radicular component as well as spinal cord compression.
- May also have associated syringomyelia, cleft palate, spina bifida, syndactyly.
- Requires surgical intervention.
- Tethered cord syndrome. Traction on the spinal cord or cauda equina.
- Bladder and bowel disturbances.

Perinatal injury

- Cerebral palsy is a result of prenatal or perinatal injury.
- It is not a developmental anomaly.
- Cerebral palsy is a non-progressive neurologic motor deficit characterized by combinations of spasticity, dystonia, ataxia or athetosis, and paresis.

Perinatal injury

- In premature infants there is an increased risk of intraparenchymal hemorrhage within the germinal matrix, often near the junction between the developing thalamus and caudate nucleus.
- Hemorrhages may remain localized or extend into the ventricular system and to the subarachnoid space.

Perinatal injury

- Infarcts may occur in the supratentorial periventricular white matter (periventricular leukomalacia), especially in premature infants.
- Chalky yellow plaques consisting of discrete regions of white matter necrosis and calcification.
- When both gray and white matter are involved by extensive ischemic damage, large destructive cystic lesions develop throughout the hemispheres (multicystic encephalopathy*).*

Perinatal injury

- In perinatal ischemic lesions of the cerebral cortex, the depths of sulci bear the brunt of injury and result in thinned-out, gliotic gyri *(*ulegyria*)*.
- The basal ganglia and thalamus may also suffer ischemic injury, with patchy neuronal loss and reactive gliosis.
- Later, aberrant and irregular myelinization gives rise to a marble-like appearance of the deep nuclei (status marmoratus).

Mental retardation

- Mental retardation and developmental deficits present in early childhood.
- One third genetic abnormality.
- Retarded are impaired in more than two of the following areas:
- Communication
- Self-care
- Home living
- Social and interpersonal skills
- Self-direction
- Academics
- Work (health and safety)
- Utilization of community resources

Hydrocephalus

- The choroid plexus within the ventricular system produces cerebrospinal fluid.
- It normally circulates through the ventricular system and enters the cisterna magna at the base of the brain stem through the foramina of Luschka and Magendie.
- Subarachnoid cerebrospinal fluid bathes the superior cerebral convexities and is absorbed by the arachnoid granulations.

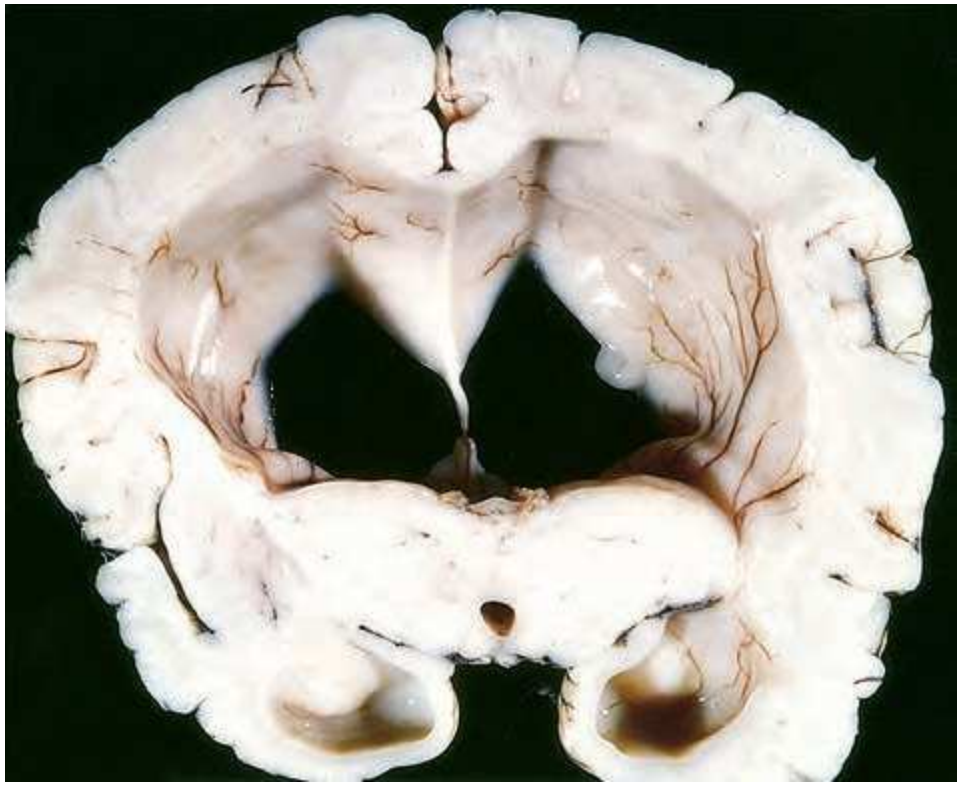
Hydrocephalus

- Hydrocephalus is the accumulation of excessive cerebrospinal fluid within the ventricular system.
- Most cases of hydrocephalus are a consequence of impaired flow and resorption of the fluid;
- Overproduction is a rare cause that can accompany tumors of the choroid plexus.
- Hydrocephalus ex vacuo refers to a compensatory increase in ventricular volume secondary to a loss of brain parenchyma.

Hydrocephalus

- Accumulation of excessive cerebrospinal fluid within the ventricular system.
- If the cranial sutures have not closed, the head enlarges.
- If the cranial sutures have not closed, neurologic changes are related to increased intracranial pressure.
- Enlargement of the ventricular system generally is seen in communicating hydrocephalus
- The ventricular system is in communication with the subarachnoid space.

Hydrocephalus



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Non-communicating hydrocephalus

- Congenital atresia of the Acquedcut of Sylvus
- Most common cause of hydrocephalus.
- Stenosis may result after ependymitis (viral infection acquired transplacentally).
- Tumor obstruction
- Shunt