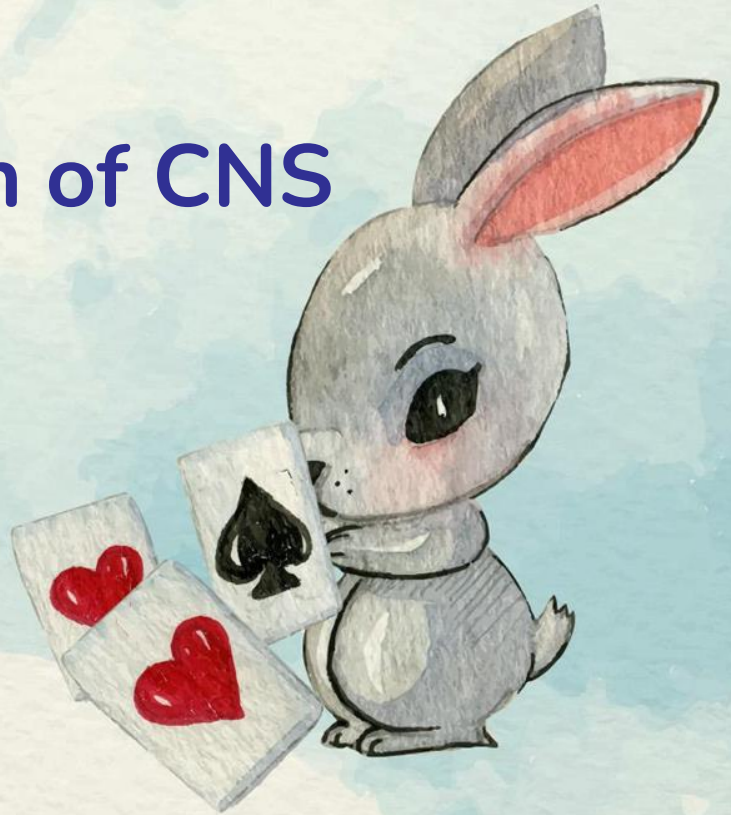
CNS Development & Congenital Malformation of CNS



R2 Warisara/Staff Peeraya

Milestones of Major Events

TABLE 1.1 Major Events in Human Brain Development and Peak Times of Occurrence

MAJOR DEVELOPMENTAL EVENT	PEAK TIME OF OCCURRENCE
Primary neurulation	3–4 weeks of gestation
Prosencephalic development	2–3 months of gestation
Neuronal proliferation	3–4 months of gestation
Neuronal migration	3–5 months of gestation
Organization	5 months of gestation to years postnatally
Myelination	Birth to years postnatally

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01

Formation of the Neural Tube

TABLE 1.2 Development of the Fundamental Craniospinal Axis—Major Phases and Peak Times of Occurrence

MAJOR DEVELOPMENTAL PHASE	PEAK TIME OF OCCURRENCE
1. Gastrulation	16–18 days p/c
2. Primary neurulation	18–26 days p/c
Neural plate formed	18 days p/c
First fusion of neural folds	22 days p/c
Anterior neuropore closes	24 days p/c
Posterior neuropore closes	26 days p/c
3. Secondary neurulation	26 days p/c—postnatal
Vacuolation-canalization	26 days—7 weeks p/c
Retrogressive differentiation	7 weeks p/c—postnatal
4. Disjunction and fusion of mesodermal-cutaneous structures	Tracks regional neural tube closure

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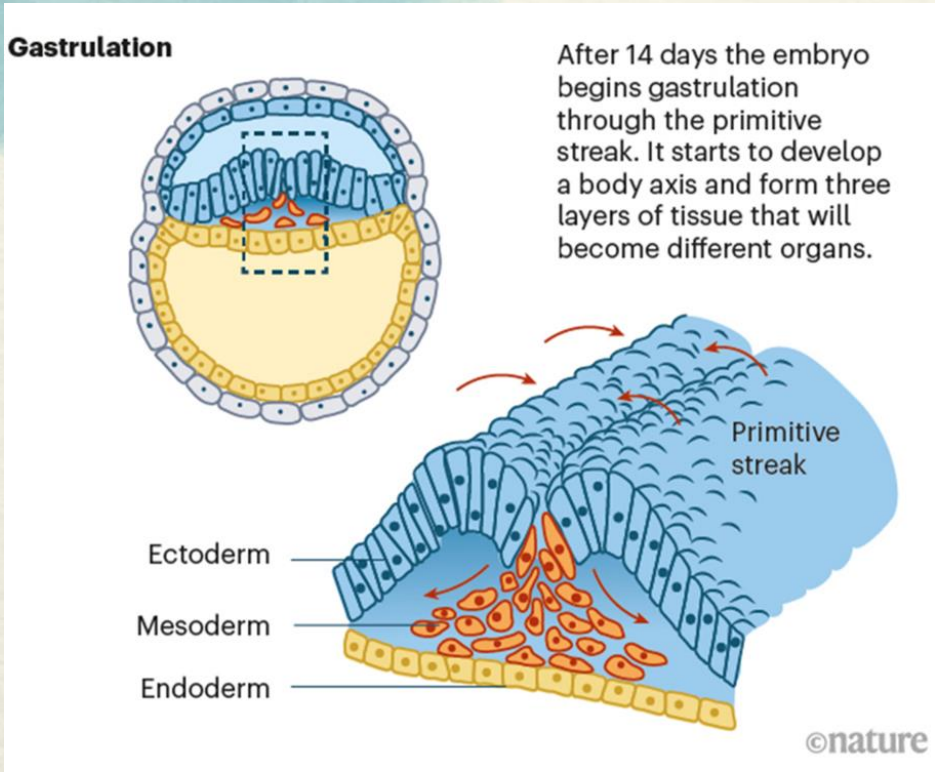
Gastrulation

16 – 18 Days p/c



- Formation of trilaminar neural plate
  - Endoderm
  - Mesoderm
  - Ectoderm
- Ectoderm
  -> Cutaneous ectoderm
  -> Neural ectoderm
- Neural ectoderm
  -> Neural plate

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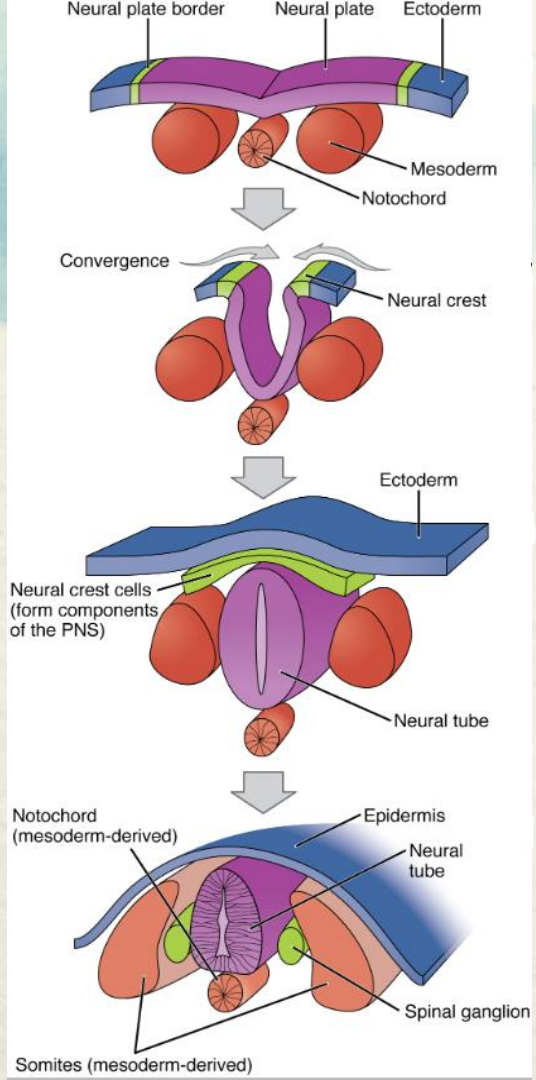

Primary Neurulation

18 – 26 Days p/c

- The lateral edges of the neural plate become elevated into neural folds.
- The neural folds continue to elevate until the edges meet in the midline to begin closure of the neural tube.
- The first fusion of the neural folds is at the level of the future hindbrain-cervical junction (foramen magnum) : 22 p/c days.

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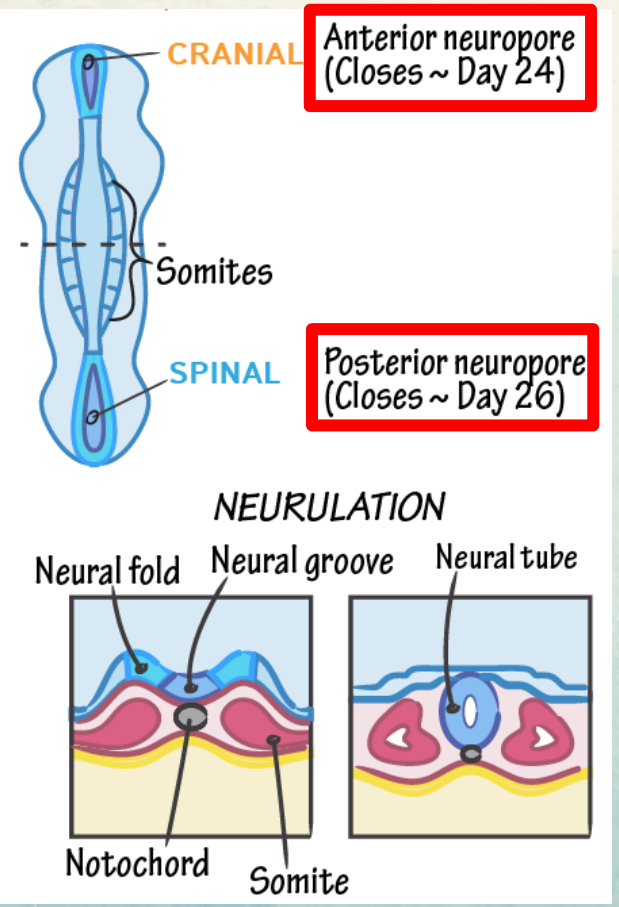
Primary Neurulation

18 – 26 Days p/c



- Closure proceeds rostrally to form the anterior neural tube (and then the brain) and caudally to form the posterior neural tube (and then the spinal cord) ; zipper-like process.

BOX 1.1 Primary Neurulation

Peak Time Period

3–4 weeks of gestation

Major Events

Notochord, chordal mesoderm → neural plate → neural tube, neural crest cells

Neural tube → brain and spinal cord → dura, axial skeleton (cranium, vertebrae), dermal covering

Neural crest → dorsal root ganglia, sensory ganglia of cranial nerves, autonomic ganglia, and so forth

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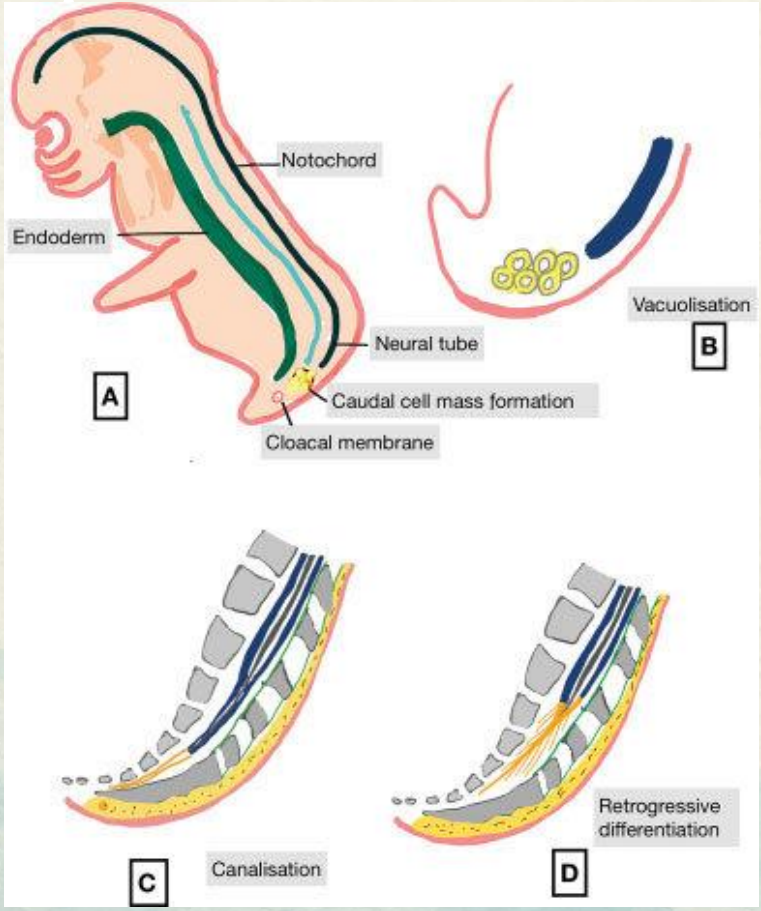
Secondary Neurulation

26 Days p/c - postnatal



- Forming the remaining sacrococcygeal neural tube -> conus medullaris, cauda equina, components of the genitourinary tract and hindgut

BOX 1.2 Secondary Neurulation (Caudal Neural Tube Formation)

Peak Time Period

Canalization: 4–7 weeks of gestation

Retrogressive differentiation: 7 weeks of gestation to after birth

Major Events

Canalization: undifferentiated cells (caudal cell mass) → vacuoles → coalescence → contact central canal of rostral neural tube

Retrogressive differentiation: regression of caudal cell mass → ventriculus terminalis, filum terminale

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02

Neural Tube Defects

Neural Tube Defects

- A disturbance in neuroectodermal development
- Defects primary or secondary neurulation

Open neural tube defects : Some continuity between the external surface of the fetus and the underlying neural tissue intermittent CSF leakage

Closed neural tube defects : Skin covered, with no exposed neural tissue and no CSF leak; the defect is confined to the spine, and other associated CNS anomalies are rare.

All women of reproductive age should take 0.4 mg (400 mcg) of folic acid per day. Women with a prior pregnancy with an NTD should take 4 mg of folic acid per day beginning 1 month before the time of planned conception and for the first 3 months of pregnancy.

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Disorders of Primary Neurulation

Order of Decreasing Severity

- Craniorachischisis totalis
- Anencephaly
- Encephalocele
- Myelomeningocele, Chiari type II malformation
- Myeloschisis

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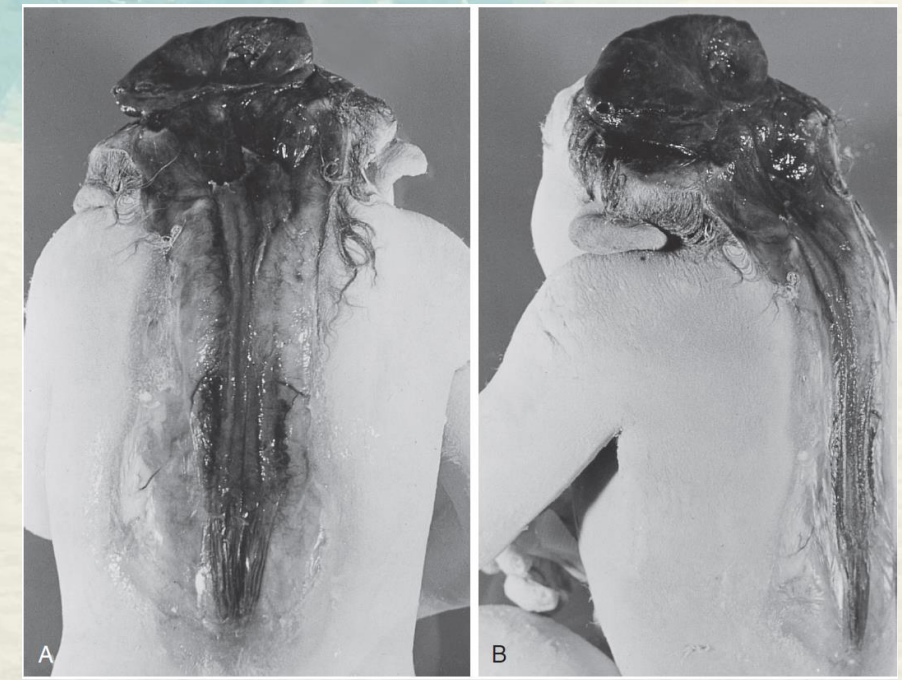
Craniorachischisis Totalis



Total failure of neurulation at a very early stage
-> an exposed neural plate–like structure (with no overlying axial skeleton or dermal covering) running down the entire dorsal extent of the central neuroaxis

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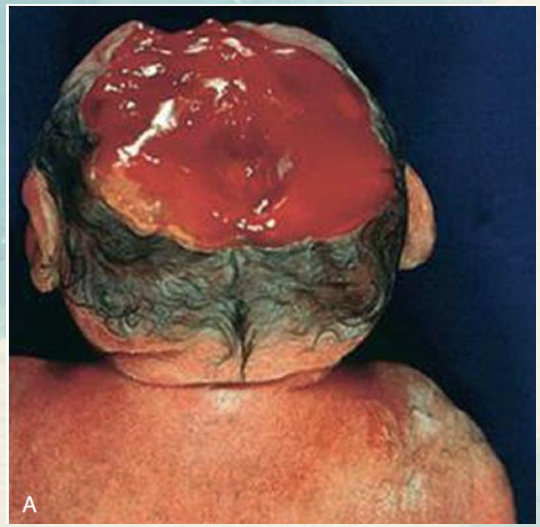

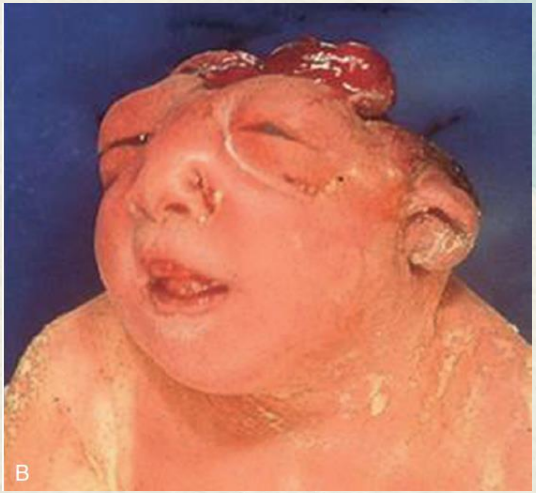

Anencephaly

- Results from (partial) absence of the cranial vault with initial protrusion of the early fetal brain above the remaining skull bones
- Most commonly involves the forebrain and upper brain stem.
- Onset of anencephaly is estimated to be no later than 24 days of gestation. Polyhydramnios is a frequent feature.
- 75% of anencephalic infants are stillborn, and the remainder die in the neonatal period.

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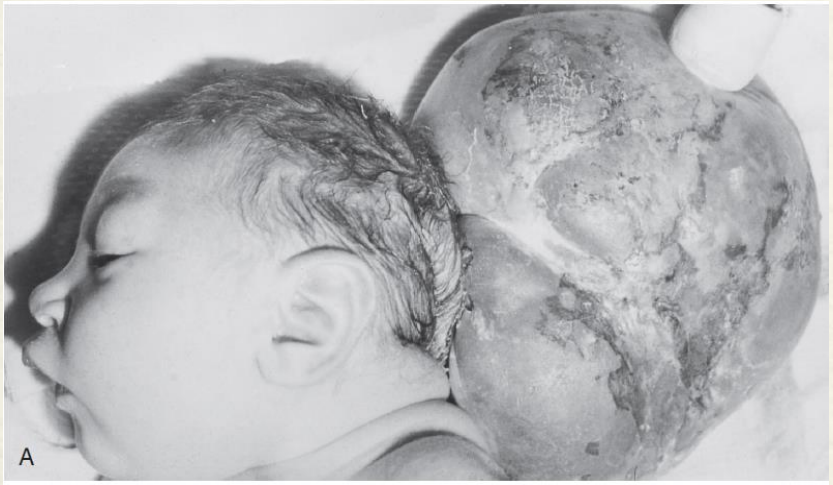

Encephalocele

- A protrusion of brain and meninges, covered by skin, through a defect in the skull
- Most commonly (70%–80%) in the occipital region.
- In Asians, the defects are usually midline-frontal.
- Prognosis varies inversely with the extent of herniated neural tissue.

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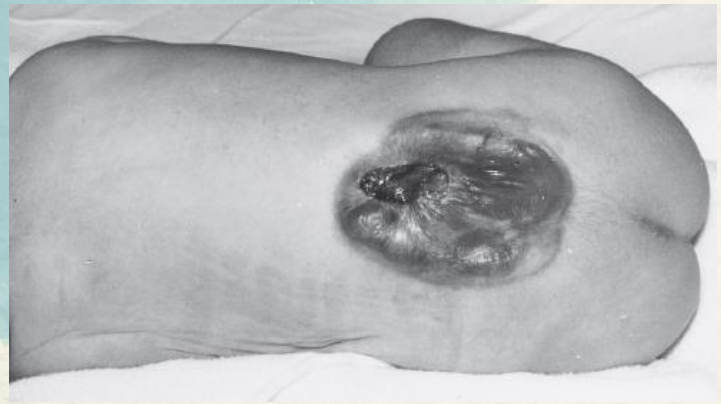
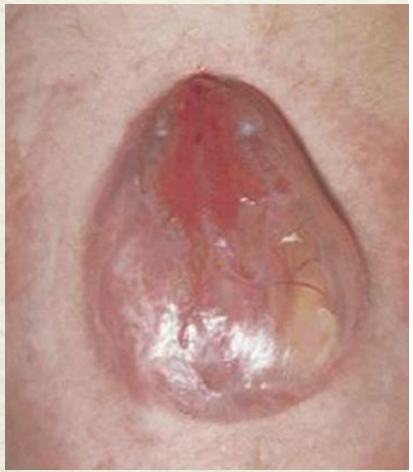
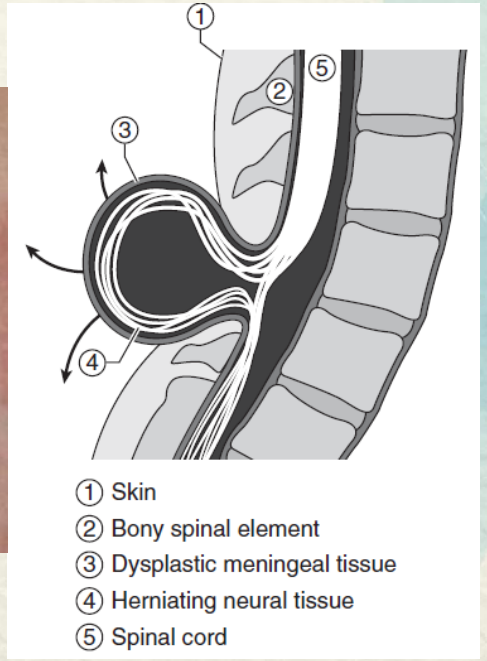
Fenichel's Clinical Pediatric Neurology, 8th Edition.

Myelomeningocele







- Herniation of neural tissue through the bony spinous defect, dorsal displacement of the cord by ventral CSF collection, cyst covered by dysplastic meningeal tissue, leakage of CSF, and lack of skin coverage.
- 80% of lesions occur in the lumbar area.

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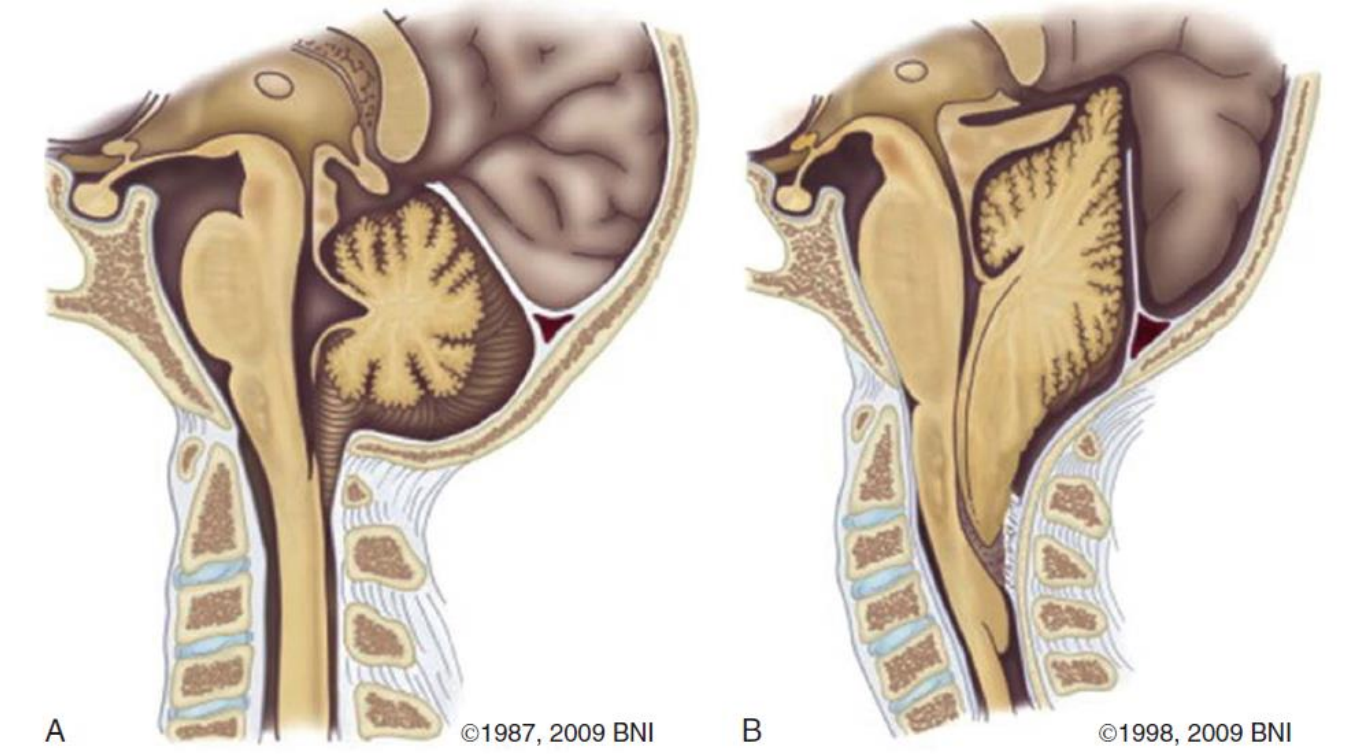
Chiari Type II Malformation



Diagrams of (A) normal posterior fossa and (B) Chiari II malformation.

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Complications of Myelomeningocele

Chiari II Malformation

Ubiquitous with lumbar-sacral myelomeningoceles

Temporal Features

Usually present by 2nd trimester

Etiological Features

Small posterior fossa is the fundamental mechanism; due to CSF leak from spinal lesion

Crowded and distorted contents

Anatomic Features

Small posterior fossa

Low-set torcular caudal herniation through foramen magnum (medulla, 4th ventricle, inferior vermis)

Rostral herniation through the tentorial notch (superior vermis)

Pressure/traction effects

Elongation and thinning of upper medulla and pons

Persistence of embryonic flexure

Cerebellar hemispheres may wrap around brain stem

Hydrocephalus due to disturbed flow dynamics from aqueduct, 4th ventricle, and subarachnoid space compression

Bony defects of foramen magnum, occiput and upper cervical vertebrae

Associated features of uncertain pathogenesis

Cerebellar dysplasia, hypoplasia or agenesis

Significant reduction of Purkinje cells

Absence of brain stem nuclei (basal pontine, olivary, other)

Clinical Importance

Stridor, apnea, cyanotic spells, and dysphagia may develop

Role in development of hydrocephalus

Hydrocephalus

Develops in 85%–90% of lumbar-sacral myelomeningoceles

Temporal Features

Most rapid progression occurring in first postnatal month

Dilation of ventricles before rapid head growth or before signs of increased intracranial pressure or both

Etiological Features

Chiari type II with obstruction of fourth ventricular outflow

Aqueductal stenosis

Impaired CSF flow through narrowed subarachnoid spaces and crowded posterior fossa

Importance

Requirement for shunt and its complications (especially infection) are a major cause of neurologic morbidity.

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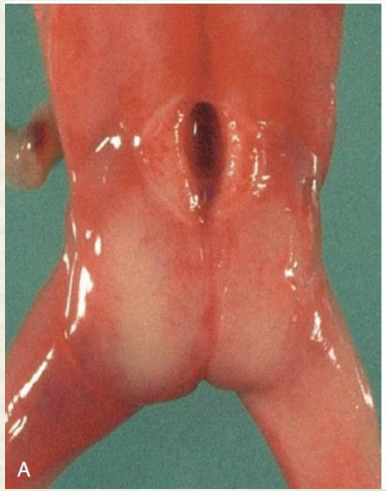

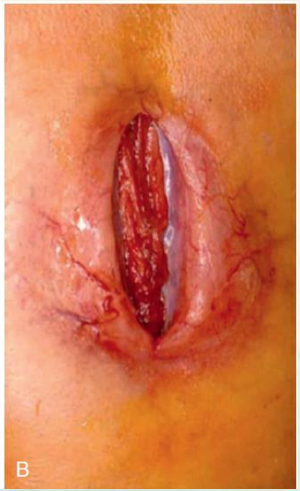

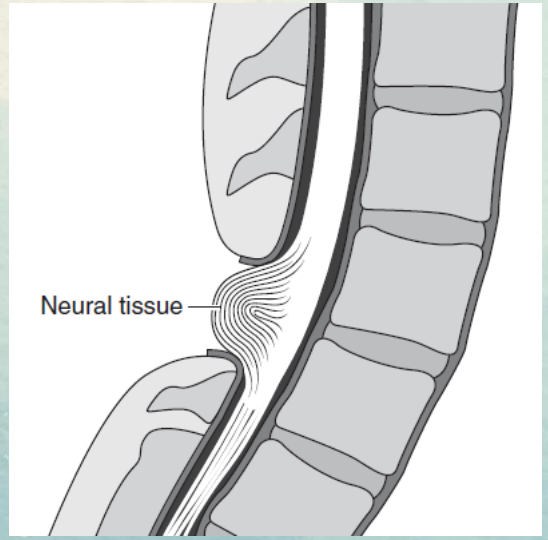

Myeloschisis

- Differs from myelomeningocele ;
  a lack of an overlying cyst of dysplastic meningeal tissue
  -> The spinal central canal continuously leaks CSF.

- Almost universally complicated by a Chiari malformation and hydrocephalus.

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Disorders of Secondary Neurulation

= closed neural tube defect
= spina bifida occulta
= occulted spinal dysraphism

Order of Time of Origin During Development

- Myelocystocele
- Meningocele-lipomeningocele
- Diastematomyelia-diplomyelia
- Lipoma, teratoma, other tumors
- Dermal sinus with or without “dermoid” or “epidermoid” cyst
- “Tethered cord” (without any of the above)

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Cutaneous Lesions Associated With Occult Spinal Dysraphism

IMAGING INDICATED

Subcutaneous mass or lipoma
Hairy patch
Dermal sinus or cyst
Atypical dimples (deep, > 5 mm, > 25 mm from anal verge)
Vascular lesion, e.g., hemangioma or telangiectasia
Skin appendages or polypoid lesions, e.g., skin tags, tail-like appendages
Scar-like lesions (aplasia cutis)

IMAGING UNCERTAIN

Hyperpigmented patches
Deviation of the gluteal fold

IMAGING NOT REQUIRED

Simple dimples (< 5 mm, < 25 mm from anal verge)
Coccygeal pits

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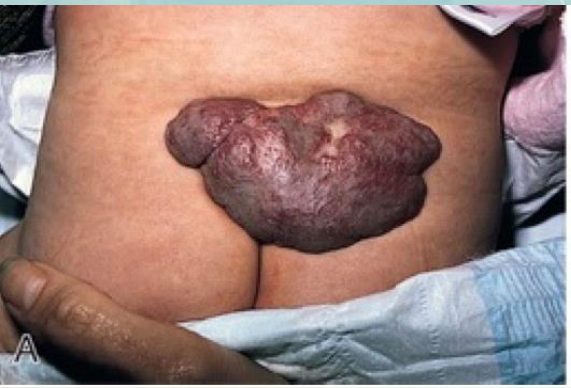

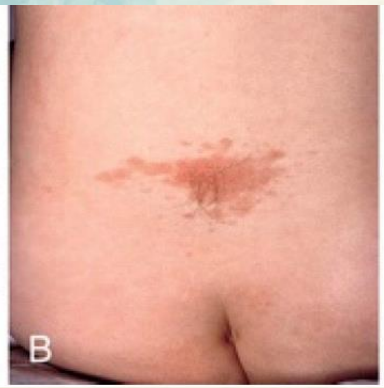

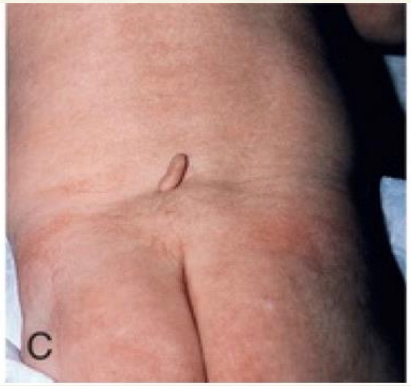

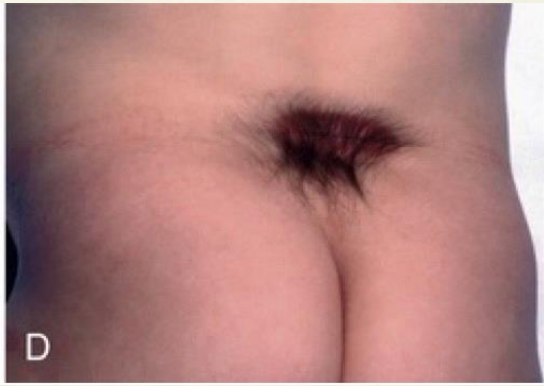

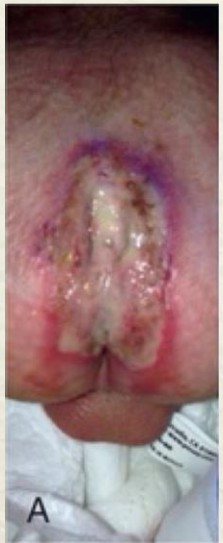

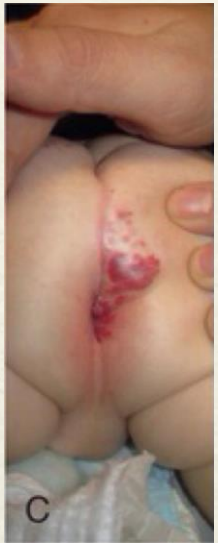

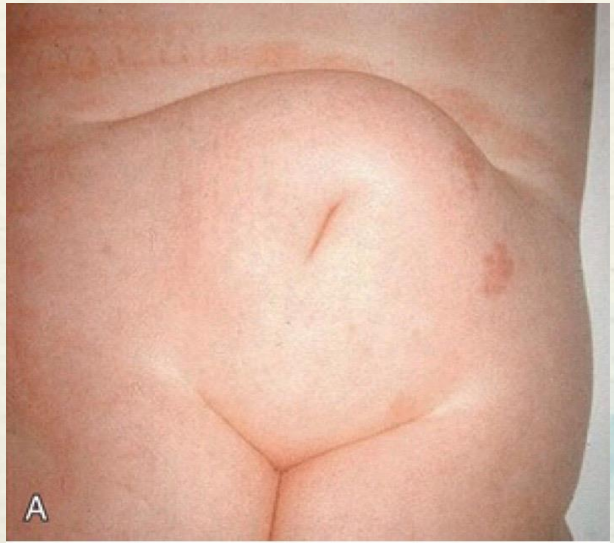

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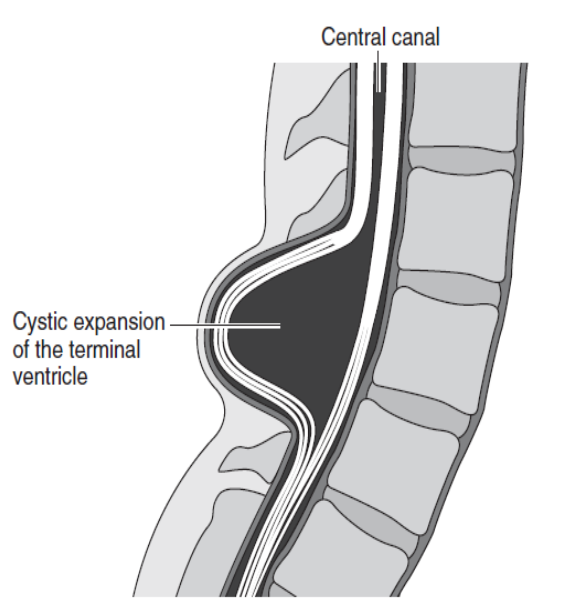

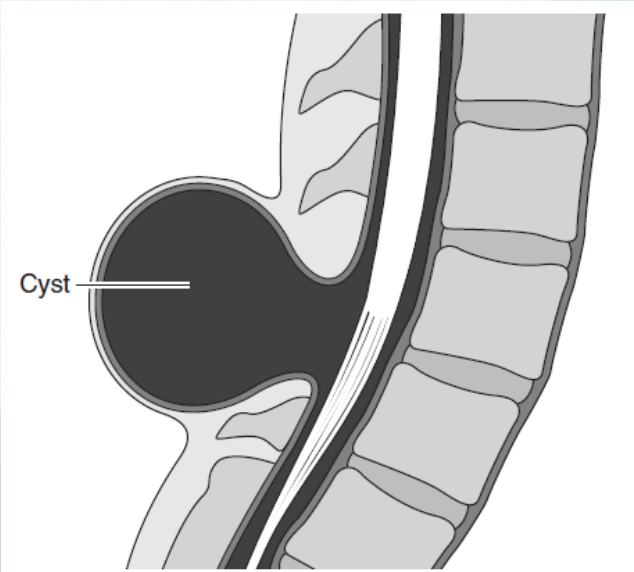

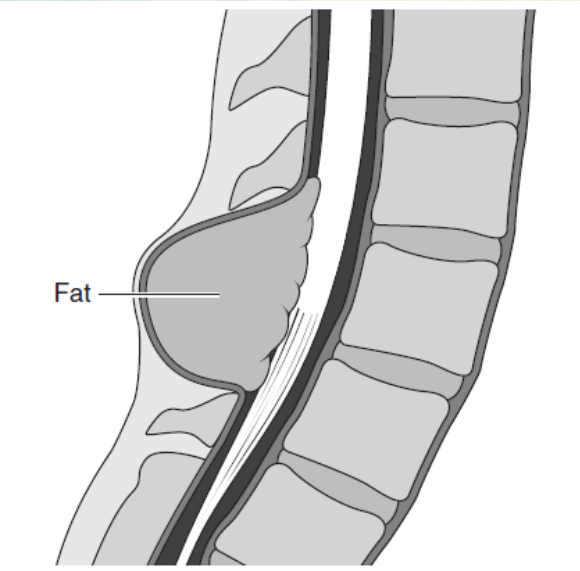

Myelocystocele : The expanded ventriculus terminalis and central canal protruding through the bony defect, which is covered by meningeal and cutaneous layers.

Meningocele : The herniation of a meningeal sac through the bony defect, without neural tissues entering into the cystic lesion. Skin covering is intact, and hence there is no CSF leak.

Lipomeningocele : Skin and dural covering, with bone defect and lipomatous mass adherent to the spinal cord elements.

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03

Prosencephalic Development

Prosencephalic Development

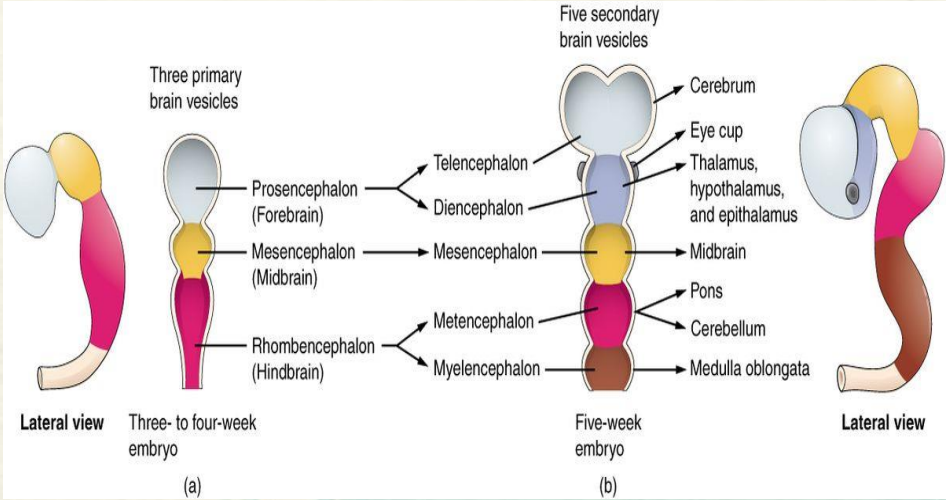
Peak Time Period : 2-3 months

Major Events

Prechordal mesoderm → face and forebrain

Prosencephalic development

1. **Prosencephalic formation**
2. **Prosencephalic cleavage**
   - Paired optic and olfactory structures
   - Telencephalon → cerebral hemispheres
   - Diencephalon → thalamus, hypothalamus
3. **Midline prosencephalic development**
   - Corpus callosum, septum pellucidum, optic nerves (chiasm), hypothalamus



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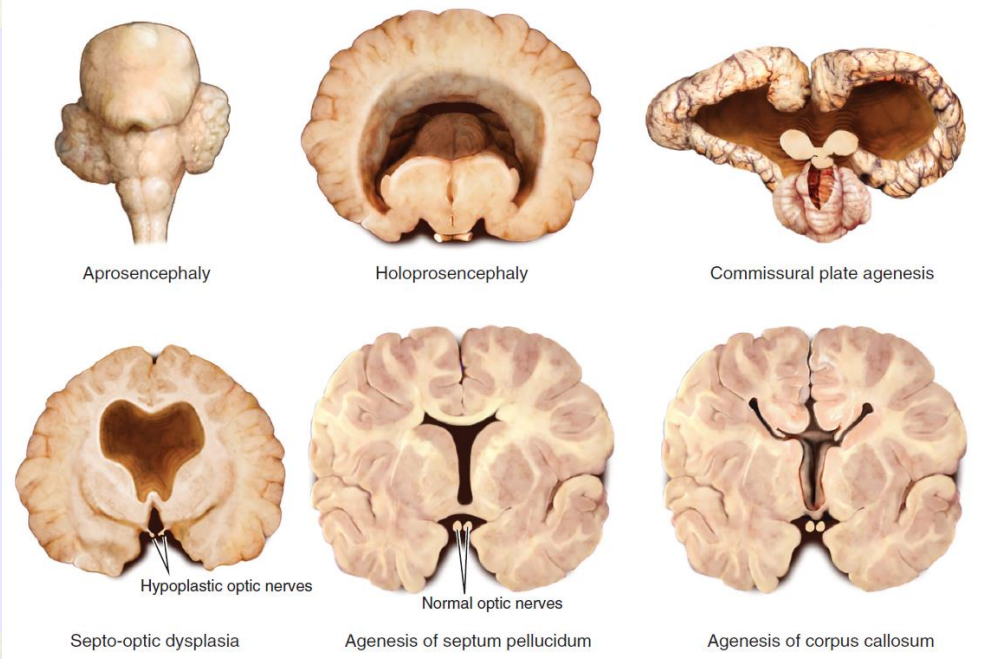
Disorders of Prosencephalic Development

Prosencephalic Formation
- Aprosencephaly/Atelencephaly

Prosencephalic Cleavage
- Holoprosencephaly/Holotelencephaly

Midline Prosencephalic Development
- Agenesis of corpus callosum
- Agenesis of septum pellucidum(with or without cerebral clefts)
- Septo-optic dysplasia
- Septo-optic–hypothalamic dysplasia



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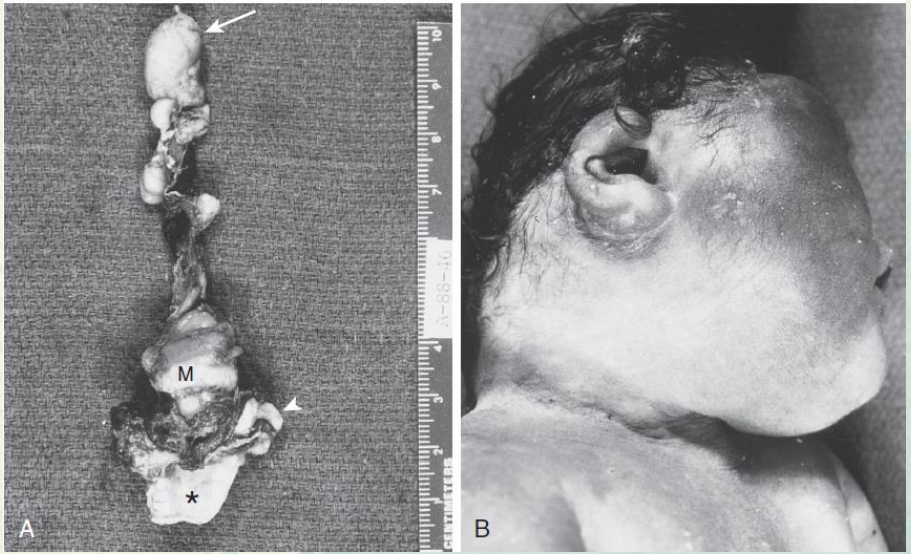
Disorders of Prosencephalic Formation

- **Aprosencephaly** :

The entire process fails to occur.
-> An absence of formation of both the telencephalon and diencephalon, with a prosencephalic remnant located at the rostral end of a rudimentary brain stem

- **Atelencephaly** :

The anomaly is less severe.
-> The diencephalon is relatively preserved.



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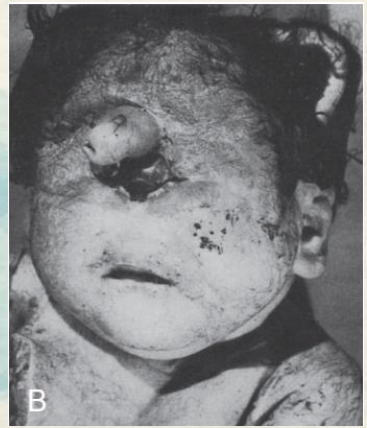
Disorders of Prosencephalic Cleavage

- **Holoprosencephaly** : The entire spectrum of cleavage disorders
- Disturbance of formation of both the telencephalon and diencephalon
- *Facial anomalies* are present in up to 80% to 90% : cyclops, proboscis, ocular hypotelorism, median cleft lip and palate, absent philtrum



BOX 2.3 Etiological Background of Holoprosencephaly[a]

Chromosomal (~60% of All Holoprosencephalies)
Chromosome 13: (~50% of chromosomal causes) trisomy 13, ring 13, deletion 13
Chromosome 18: trisomy 18, ring 18, deletion 18
Chromosomes 2,3,7,21: deletions, trisomies

Monogenic Syndromic (~25% of All Holoprosencephalies)
Smith-Lemli-Opitz (AR)
Pseudotrisomy 13 (AR)

Monogenic Nonsyndromic (~13% of All Holoprosencephalies)
Mutations in SHH, PTCH, GLI2, SIX3, TGIF, TDGF1, FAST1, Z1C2, DLL1, DISP1, FOXH1

Teratogenic Agents
Meckel (AR)
Velocardiofacial (AD)
Pallister-Hall (AD)
Maternal diabetes
Impaired cholesterol biosynthesis
Others

Sporadic

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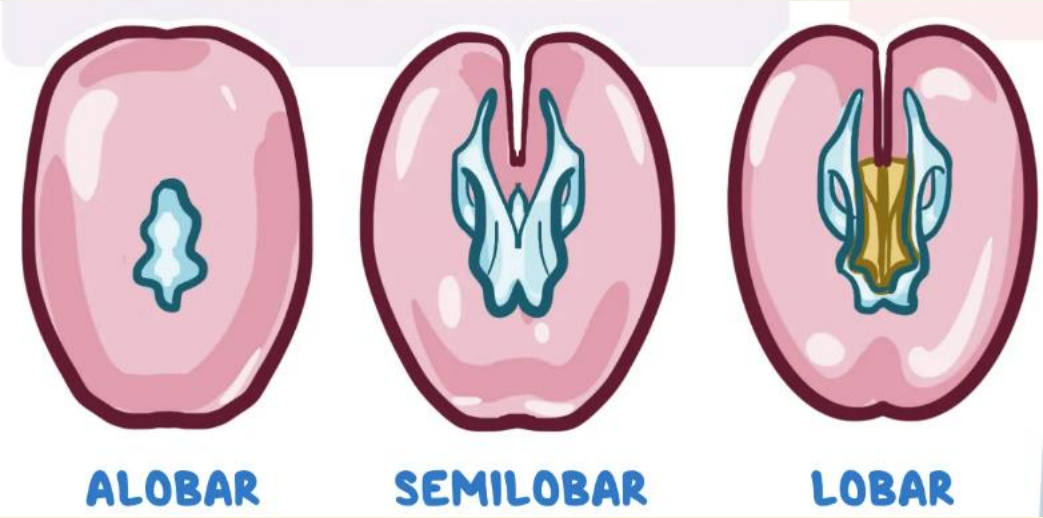

VENTRICLES
CORPUS CALLOSUM
CEREBRUM

	ALOBAR	SEMILOBAR	LOBAR
Cerebral non-separation	Diffuse (holosphere)	Frontal	Rostroventral frontal
Corpus callosum	Absent	Splenium present Rostrum, genu, and body absent	Splenium present Rostrum and genu absent Anterior body variably present
IHF and falx	Completely absent	Absent anteriorly Present posteriorly	Hypoplastic anteriorly Present posteriorly
Ventricles	Monoventricle communicating widely with dorsal cyst	Anterior horns absent Posterior horns present Small third ventricle	Anterior horns rudimentary Third ventricle formed

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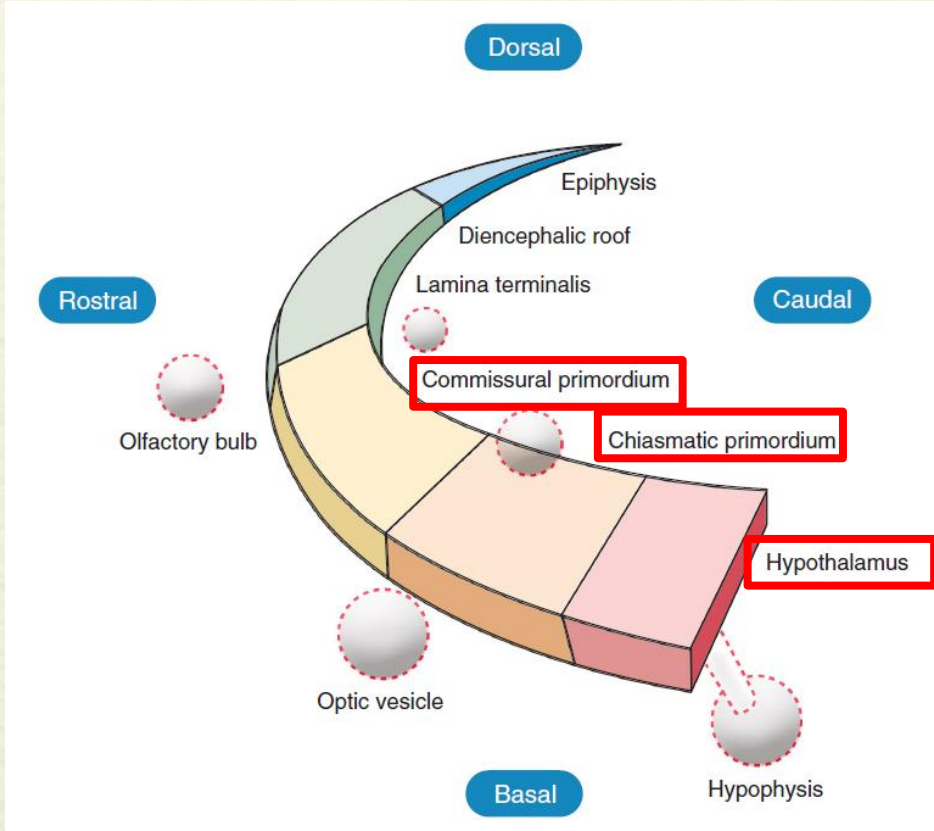
Disorders of Midline Prosencephalic Development

TABLE 2.2 Disorders of Midline Prosencephalic Development

REGION AFFECTED	DISORDER
Commissural plate	Agenesis of corpus callosum and/or septum pellucidum
Commissural and chiasmatic plates	Septo-optic dysplasia
Commissural, chiasmatic, and hypothalamic plates	Septo-optic–hypothalamic dysplasia



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Agenesis of the Corpus Callosum

- Partial or complete and isolated or complex (associated with other central nervous system [CNS] anomalies, dysmorphic syndromes, chromosomal or genetic defects, or acquired infectious or vascular lesions).
- Without other recognized abnormality of the CNS -> can be asymptomatic.
- 85% had cognitive deficits, and more than 90% had neuromotor disturbances.

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BOX 2.4 Conditions Associated With Callosal Agenesis

Autosomal Recessive Syndromes
- Walker-Warburg syndrome
- Fukuyama muscular dystrophy
- Joubert syndrome
- Andermann syndrome
- Meckel syndrome

Autosomal Dominant Syndromes
- Familial septo-optic dysplasia
- Sotos syndrome
- Rubenstein-Taybi syndrome
- Lissencephaly type I (LIS1)

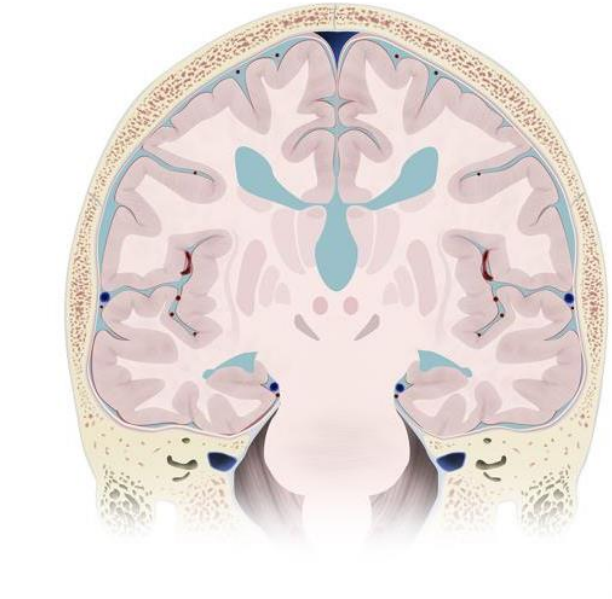
X-Linked Syndromes
- X-linked lissencephaly with ambiguous genitalia (XLAG)
- X-linked lissencephaly (XLIS)
- Aicardi syndrome
- CRASH syndrome spectrum (L1CAM gene mutations) (**c**allosal agenesis, **r**etardation, **a**dducted thumbs, **s**huffling gait, **h**ydrocephalus)
  - Hydrocephalus due to stenosis of the aqueduct of Sylvius (HSAS)
  - Mental retardation, aphasia, shuffling gait, and adducted thumbs (MASA)

Metabolic Disorders
- Nonketotic hyperglycinemia
- Pyruvate dehydrogenase complex deficiency
- Fumarase deficiency

Other Central Nervous System Anomalies
- Myelomeningocele with Chiari II malformation
- Vermian hypoplasia
- Neuronal migration disorders

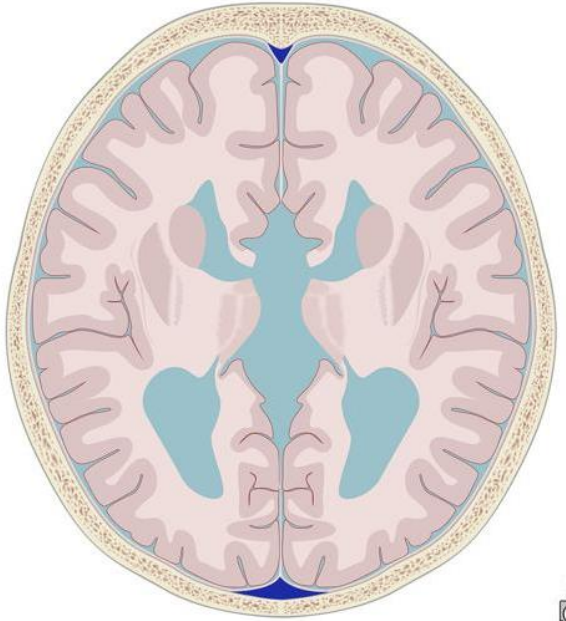
Moose head appearance

of corpus callosum agenesis



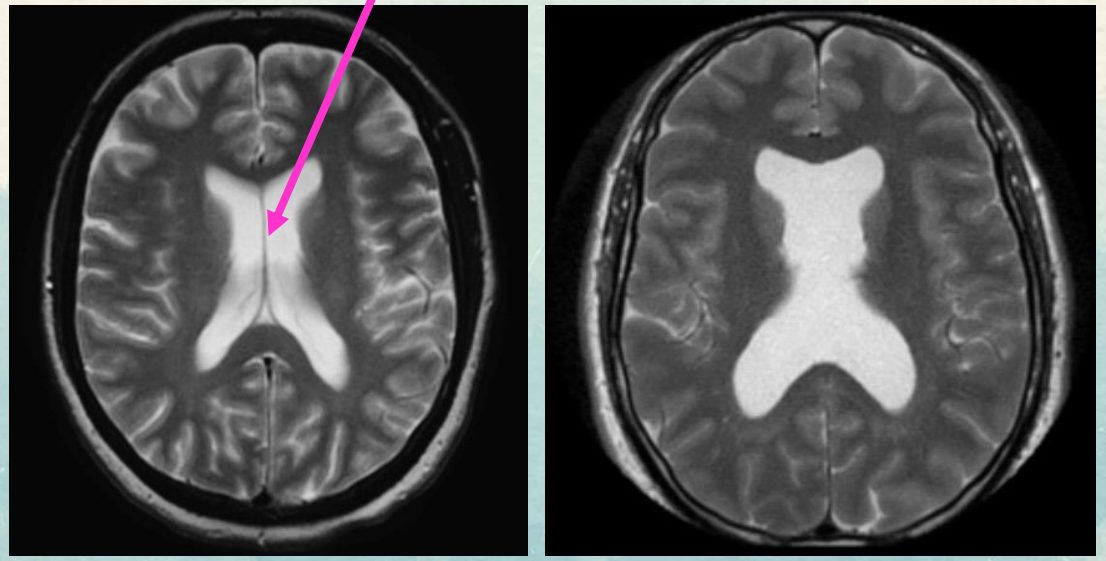
Racing car sign

of corpus callosum agenesis



Absence of the Septum Pellucidum

- Never seen as an isolated finding.
- It was associated with holoprosencephaly, agenesis of the corpus callosum, septo-optic dysplasia, schizencephaly, basilar encephalocele, hydrocephalus (as a result of aqueductal stenosis or the Chiari II malformation), and porencephaly-hydranencephaly.



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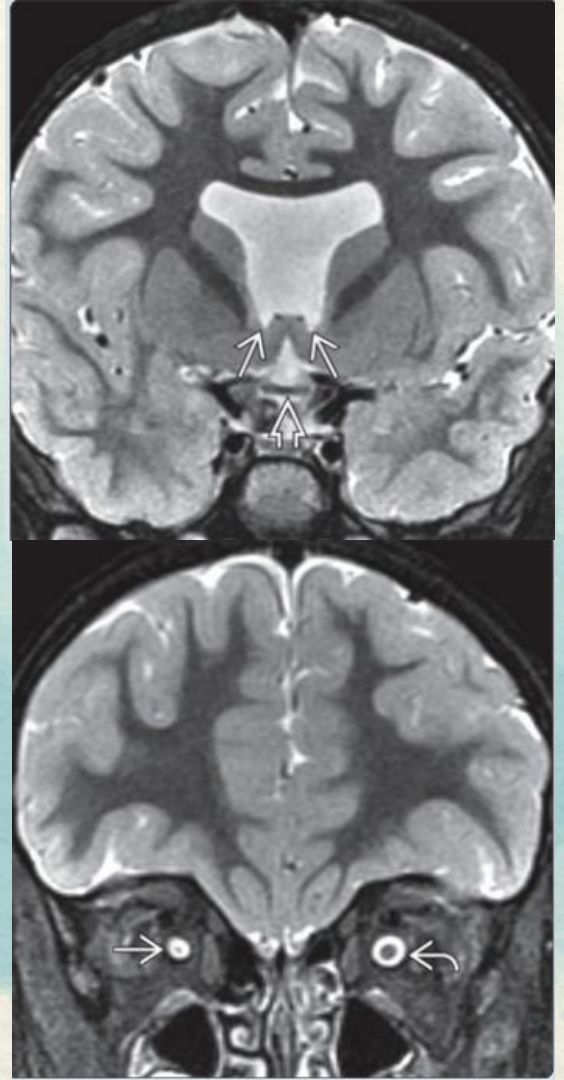
Septo-optic dysplasia

- Absent septum pellucidum
- Optic nerve hypoplasia
- Disturbances of hypothalamic-pituitary function
  - 60% exhibited diabetes insipidus
  - 80% had multiple pituitary hormone deficiencies
  - 60% had genital anomalies resulting from hypogonadotrophic hypogonadism
  - 75% had persistent neonatal hypoglycemia



04

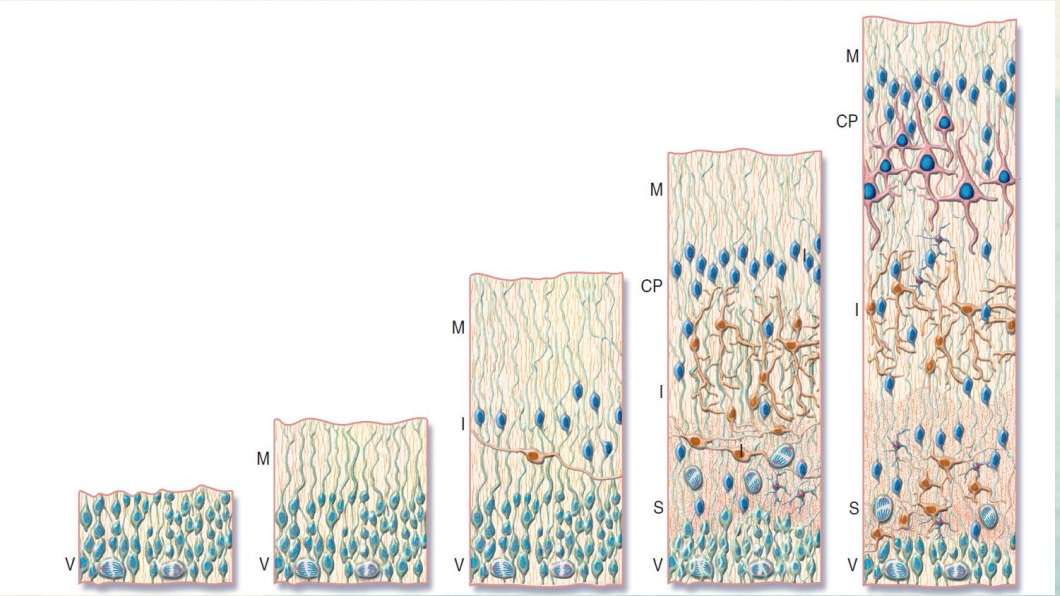
Neuronal Proliferation

Neuronal Proliferation

Peak Time Period : 3-4 months

Major Events

- Ventricular and subventricular zones are the sites of proliferation.
- Proliferative units are produced by symmetrical divisions of progenitor cells.
- Proliferative units later enlarge by asymmetrical divisions of progenitor cells before neuronal migration.



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Microcephaly

Autosomal recessive (microcephaly vera)
Autosomal dominant
X-linked recessive
Genetics as yet undetermined

Teratogenic
Irradiation
Metabolic-toxic (e.g., fetal alcohol syndrome, related to cocaine, hyperphenylalaninemia)
Infection (rubella, cytomegalovirus, HIV, Zika virus)

Syndromic (Multiple Systemic Anomalies)
Chromosomal
Familial
Sporadic

Sporadic (Nonsyndromic)

---

[a]Excluded are cases of congenital microcephaly secondary principally to destructive disease (hypoxia-ischemia, infection) developing after the conclusion of cerebral neuronal proliferation.

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Macrocephaly

Isolated Macrocephaly
Familial
Autosomal dominant (relation to "benign enlargement of extracerebral spaces" or "external hydrocephalus")
Autosomal recessive
Sporadic

Associated Disturbance of Growth
Achondroplasia
Beckwith syndrome
Cerebral gigantism
Fragile X syndrome (see the section on chromosomal disorders, below in the box)
Marshall-Smith syndrome
Thanatophoric dysplasia
Weaver syndrome

Neurocutaneous Syndromes
Multiple hemangiomatoses
Lipomas, hemangiomas, lymphangiomas, pseudopapilledema (Bannayan-Riley-Ruvalcaba)
Asymmetrical hypertrophy, hemangiomata, varicosities (Klippel-Trenaunay-Weber)
Asymmetrical hypertrophy, telangiectatic lesions, flame nevus of the face (cutis marmorata, telangiectatica congenita)
Neurofibromatosis,[a] tuberous sclerosis,[b] Sturge-Weber syndrome[b]
Epidermal nevus syndrome (see the section on unilateral macrocephaly, below)

Chromosomal Disorders
Fragile X syndrome (relative macrocephaly)
Klinefelter syndrome

Unilateral Macrocephaly (Hemimegalencephaly)
Isolated
Syndromic: epidermal nevus syndrome, Proteus syndrome (most common)

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05
Neuronal Migration

Neuronal Migration

Peak Time Period : 3-5 months

Major Events

Cerebrum

- Radial migration: cerebral cortex (projection neurons), deep nuclei
- Tangential migration: cerebral cortex (interneurons)

Cerebellum

- Radial migration: Purkinje cells, dentate nuclei
- Tangential migration: external → internal granule cells

"The series of events whereby millions of neurons move from their sites of origin in the ventricular and subventricular zones to the loci within the CNS, where they will reside for life."

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Disorders of Neuronal Migration

Order of Decreasing Severity

- Schizencephaly
- Agyria-pachygyria spectrum ; Lissencephaly
- Polymicrogyria
- Heterotopia—periventricular, subcortical

‘Seizures’ are most often the dominant early neurological sign with the more severe migrational disturbances.

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Schizencephaly

- The presence of unilateral or bilateral clefts within the cerebral hemispheres.
- The cleft may be fused or unfused.
- The borders of the cleft may be surrounded by abnormal brain, particularly microgyria.
- When the clefts are bilateral, many patients are severely intellectually challenged, with seizures that are difficult to control, and microcephaly with spastic quadriparesis.
- Unilateral schizencephaly is a common cause of congenital hemiparesis.

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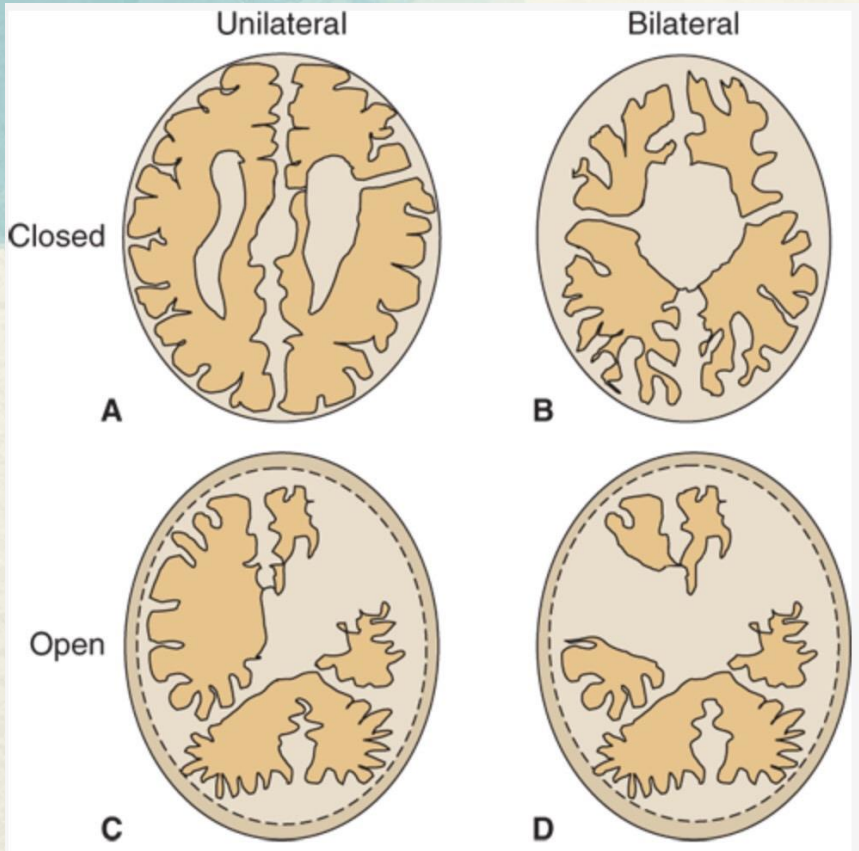
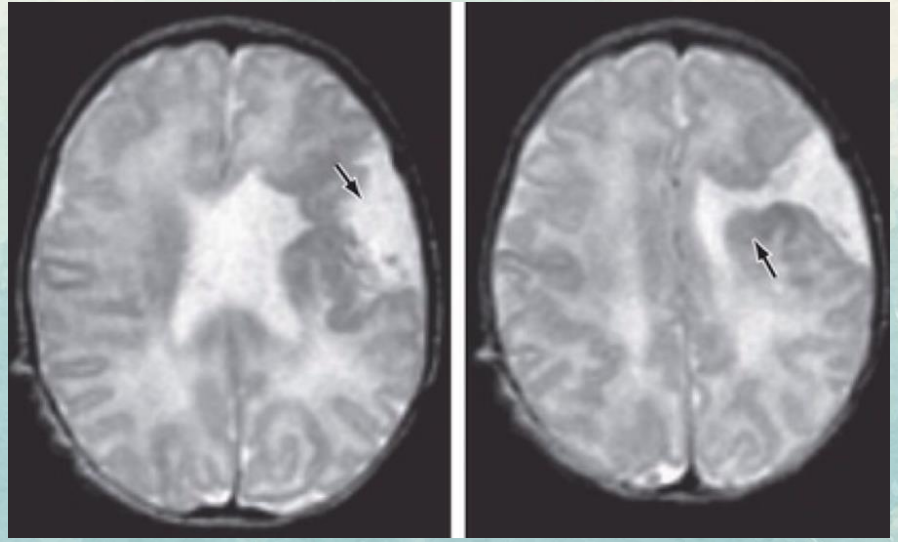
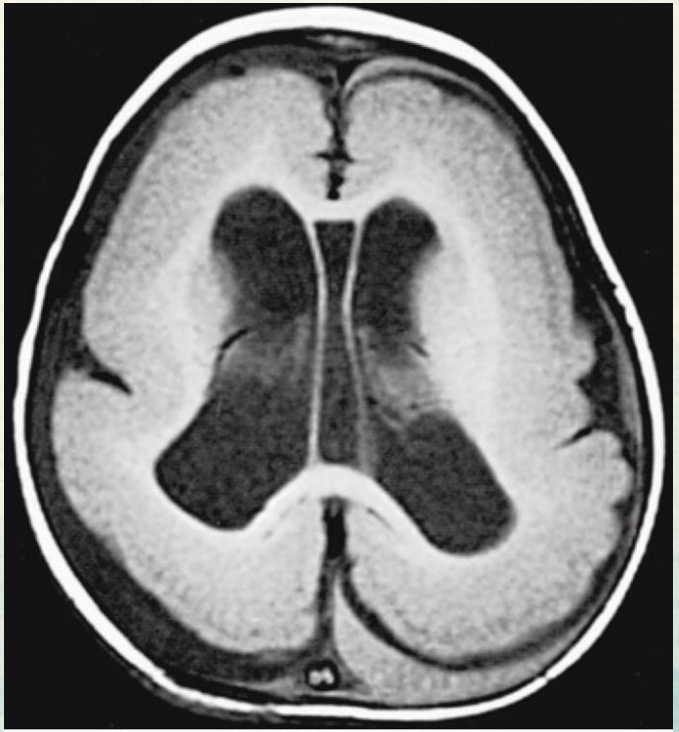

Unilateral
Bilateral
Closed
Open
A
B
C
D



Lissencephaly

- Agyria, Smooth brain
- Absence of cerebral convolutions and poorly formed sylvian fissure, giving the appearance of a 3- to 4- mo fetal brain.
- Failure to thrive
- Microcephaly
- Marked developmental delay
- Severe seizure disorders
- Ocular abnormalities are common, including optic nerve hypoplasia and microphthalmia.



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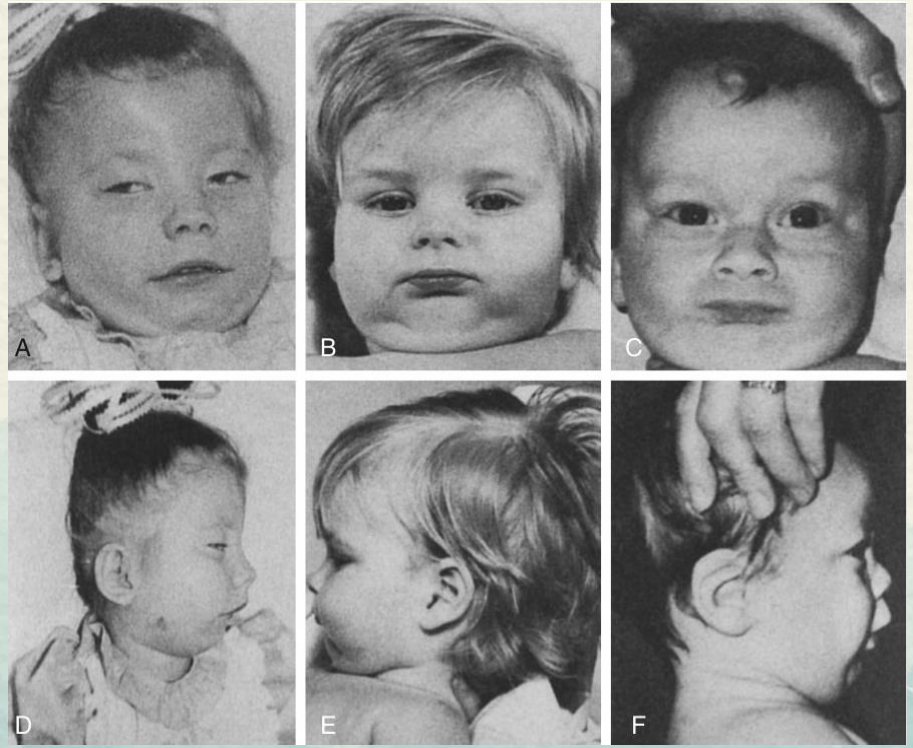
Miller-Dieker syndrome



- 15% of lissencephaly cases
- Related to the chromosome 17p13.3 locus
- Characteristics facial appearance with a short nose with upturned nares, a long and protuberant upper lip with a thin vermilion border, and a relatively flattened midface

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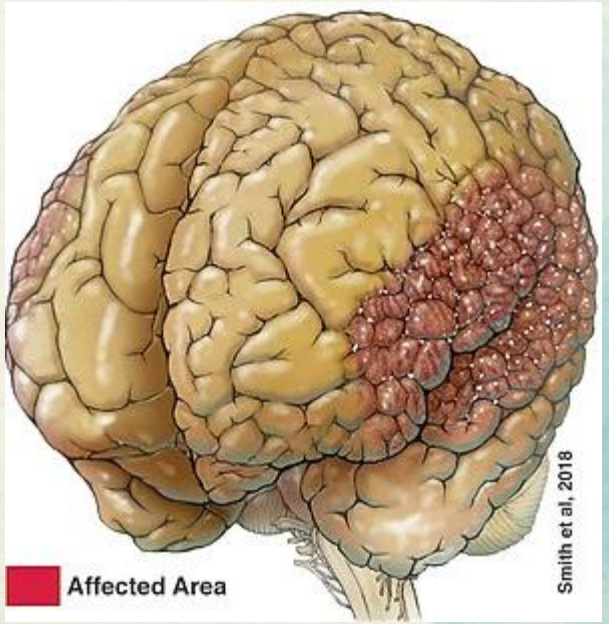
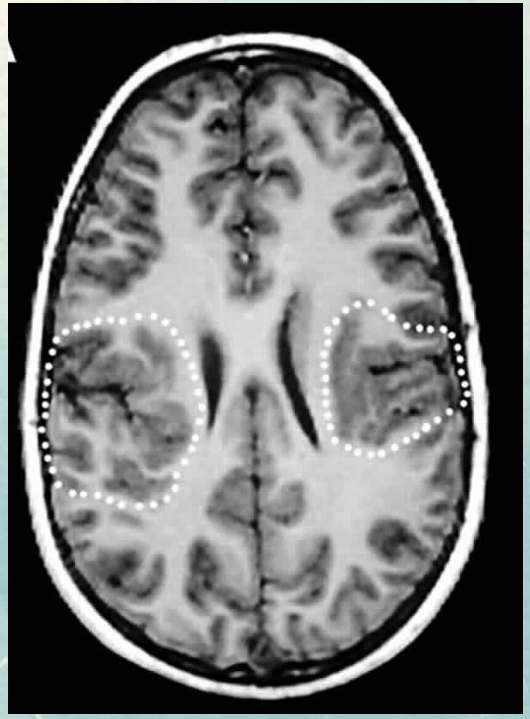
Polymicrogyria

- An augmentation of small convolutions separated by shallow enlarged sulci
- Epilepsy, including drug-resistant form, is a common feature.





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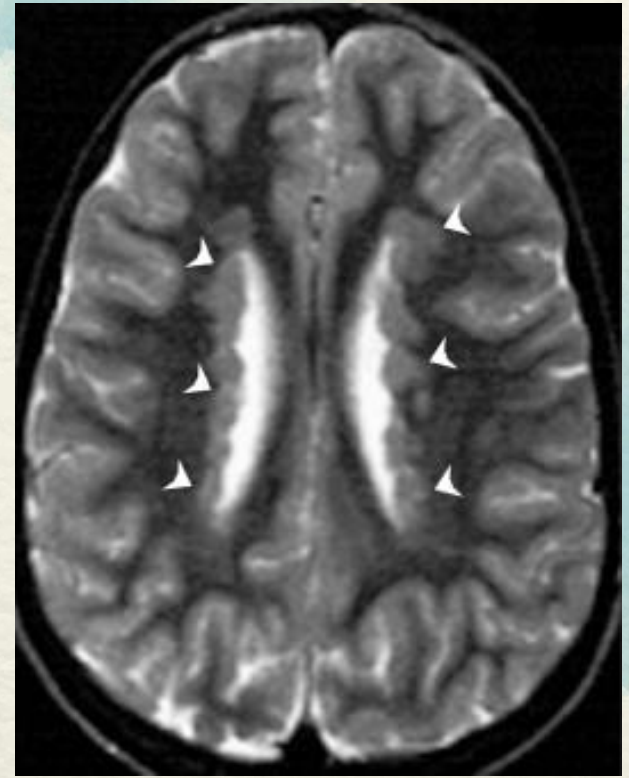
Heterotopia



- Collections of nerve cells in the periventricular region or in subcortical white matter that are apparently arrested during radial migration from the subependymal germinative zones.
- Intractable seizures are a common features.

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06
Organization

Organization

Peak Time Period : 5 months' gestation – years postnatal

Major Events

1. Establishment and differentiation of the subplate neurons
2. Attainment of proper alignment, orientation, and layering (lamination) of cortical neurons
3. Gyral development
4. Elaboration of dendritic and anoxal ramification
5. Establishment of synaptic contacts
6. Cell death and selective elimination of neuronal processes and synapses
7. Proliferation and differentiation of glia

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Disorders of Organization

- Disorders of subplate neurons
- Disorders of lamination
- Disorders of gyrification
- Disorders of dendrites and synaptogenesis
  - Mental retardation (idiopathic), with or without seizures
  - Rett syndrome
  - Autism spectrum disorder
  - Fragile X syndrome
  - Down syndrome

- Disorders of anoxal outgrowth
  - Agenesis of corticospinal tracts
  - Congenital cranial disinnervation disorders
- Disorders of glial proliferation and differentiation
- Disorders of multiple organizational events delineated in vivo
  - Prematurity-related factors
  - Nutritional factors
  - Experiential factors

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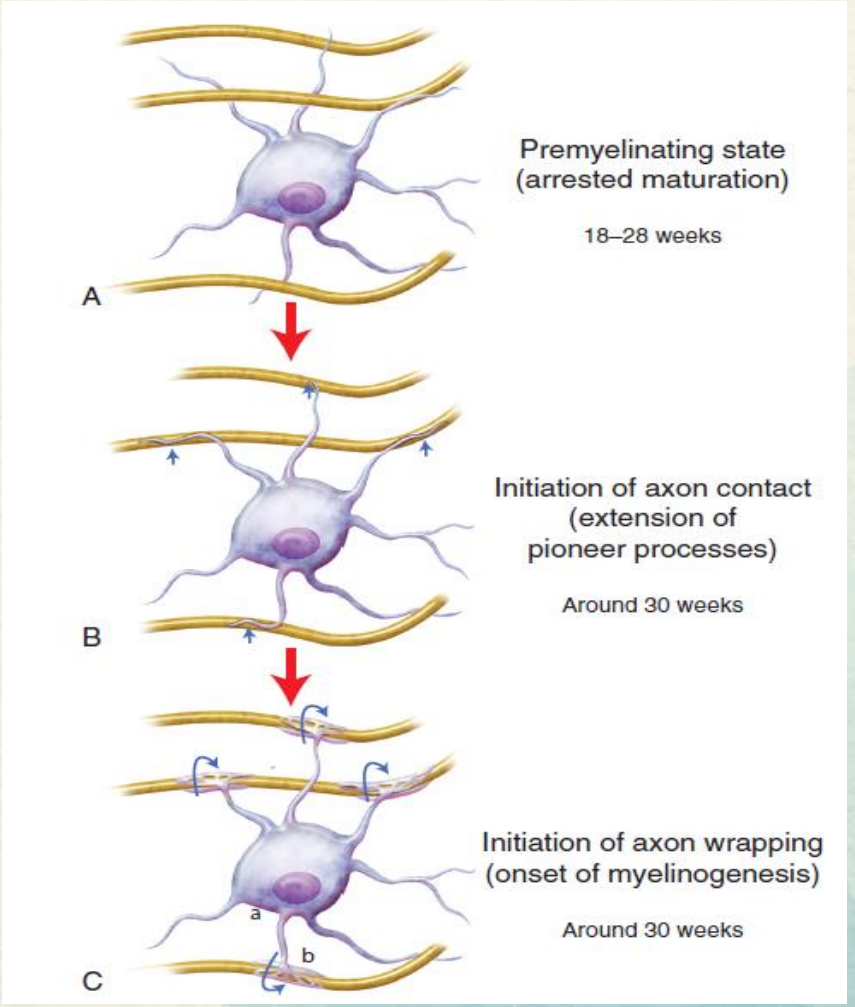
07
Myelination

Myelination

Peak Time Period
Birth to years postnatal
Major Events
Oligodendroglial proliferation, Migration,Differentiation, and Alignment
→ Myelin sheaths



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Disorders of Myelination

- Cerebral white matter hypoplasia
- Prematurity-related factors
  - Periventricular leukomalacia/ Cerebral white matter injury
  - Other factors
- Nutritional factors
  - Undernutrition
  - Breast-feeding
  - Iron deficiency

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Summary

CNS Developmental Stages	Timing	Associated Anomalies
Primary neurulation	3-4 weeks	Craniorachischisis totalis, Anencephaly Myelomeningocele, Encephalocele, Myeloschisis
Secondary neurulation	4-7 weeks	Myelocystocele, Meningocele, Lipomeningocele, Lipoma, Teratoma, Dermal sinus, Tethered cord
Prosencephalic development	2-3 months	Aprosencephaly, Holoprosencephaly, Agenesis of corpus callosum, Agenesis of septum pellucidum, Septo-optic dysplasia
Neuronal proliferation	3-4 months	Microcephaly, Macrocephaly
Neuronal migration	3-5 months	Schizencephaly, Lissencephaly, Polymicrogyria, Heterotopia
Organization	5 months - years	Mental retardation, Rett syndrome, Down syndrome, Autism spectrum disorder, Fragile X syndrome, Prematurity
Myelination	Birth - years	Cerebral white matter hypoplasia, Prematurity, Undernutrition

Take Home Message

- Timeline of CNS developmental events and peak time of occurrence
- CNS developmental stages and associated anomalies
- The presentation and imaging of congenital CNS malformation

Thanks