Overview of Brain Development

With thanks to Dr Volpe and his text

Major events in brain development

- Primary neurulation: 3-4 wks
- Prosencephalic development: 2-3 mo
- Neuronal proliferation: 3-4 mo
- Neuronal migration: 3-5 mo
- Organization: 5+ mo
- Myelination: Birth+

Primary Neurulation

- Notochord -> neural plate -> neural tube, neural crest
- Neural tube -> brain and spinal cord
- Neural crest -> dorsal, sensory, autonomic ganglia
Secondary neurulation

- Formation of caudal neural tube by canalization at 4-7 wks
- Vacuolization -> coalescence -> central canal
- Regression of caudal cell mass -> conus medullaris, filum terminale (7 wks until after birth)

Neural tube defects

- Order of decreasing severity-
  1) Craniorachischisis totalis
  2) Anencephaly
  3) Myeloschisis
  4) Encephalocele
  5) Myelomeningocele

Anencephaly

- Essentially, a fatal condition with nearly 100% mortality in the 1st months of life. In the past, discussions of the definition of brain death occurred with the thought that these patients could be used as heart donors in transplant programs
Myelomeningocele

• L1 to L2 with hip flexion
• L3 to L4 with hip adduction and knee extension
• L5 to S1 with knee flexion, ankle dorsiflexion, ankle plantar flexion
• S1 to S4 with toe flexion

Myelomeningocele

• Approximately ¾ with brain stem malformations (e.g., poor myelination, hypoplastic cranial nerve nuclei, pontine nuclei)
• Approximately 90% with cerebral cortical dysplasia (e.g., heterotopias, polymicrogyria)
• Hydrocephalus with Arnold-Chiari in nearly all cases LS and above
Occult dysraphic states

- Disorders of caudal formation (by time of development)
- 1) Myelocystocele
- 2) Diastematomyelia
- 3) Meningocele-lipomeningocele
- 4) Lipoma
- 5) Dermal sinus
- 6) Tethered cord

Features of occult state

- Abnormal hair collection
- Subcutaneous mass
- Hemangioma, skin tag
- Cutaneous dimple or tract

Prosencephalic Development

- Occurs at 2-3 mo
- Prechordal mesoderm -> face, forebrain
- Prosencephalic development-
  1) Prosencephalic formation
  2) Prosencephalic cleavage ->optic/olfactory structures, cerebral hemispheres, thalamus, hypothalamus
  3) Midline prosencephalic development of corpus callosum, septum pellucidum, optic nerves, hypothalamus
Disorders of Prosencephalic Development

- Prosencephalic formation- aprosencephaly, atelencephaly
- Prosencephalic cleavage- holoprosencephaly, holotelencephaly
- Midline prosencephalic development- agenesis of corpus callosum, agenesis of septum pellucidum, septo-optic dysplasia

Disorders of Midline Prosencephalic Development

- In development, 3 midline plates of tissue thicken. If commisural development effected -> agenesis of corpus callosum +/or septum pellucidum. If commisural + chiasmatic plate, septo-optic dysplasia. If commisural, chiasmatic, and hypothalamic plates, septo-optic hypothalamic dysplasia.
Aicardi Syndrome

- Female 100%
- Chorioretinal lacunae 100%
- Agenesis of corpus callosum 100%
- Seizures 100%
- Infantile spasms 70%
- Cerebral cortical heterotopias 50%
- Costovertebral defects 50%

Neuronal Proliferation

- Peaks at 3-4 mo
- Early peak, app 2-4 mo, neurons and radial glia (involved in migration). Later peak, 5+ mo, glia. Neurons proliferate by to-and-fro migration in ventricular zone. Some also are generated in the subventricular zone. Proliferative units are produced by symmetric division of stem cells. Units later enlarge by asymmetric division before migration.
Disorders of Proliferation - Micrencephaly

- Decreased # proliferative units - radial microbrain - rare with unclear genetics
- Decreased size of proliferative units - micrencephaly vera - familial (autosomal recessive, dominant, x-linked), teratogenic (radiation, FAS, rubella, etc), sporadic

Disorders of Proliferation - Macrencephaly

- Isolated - some related to benign enlargement of extra cerebral spaces
- Associated with growth disturbance - eg cerebral gigantism, achondroplasia
- Neurocutaneous - some, eg neurofibromatosis, with glial proliferation
- Chromosomal - ? Fragile X
- Unilateral macrencephaly

Migration

- Peak period - 3-5 mo
- In cerebrum, occurs by radial migration. In cerebellum, both radial (Purkinje, dentate) and tangential (granular)

Cortical Migration

- Neurons follow radial glial guides
- Early neurons take place deep to late arriving neurons
- Later, radial glia proliferate and differentiate into astrocytes
Migrational Disorders

- Clinical correlates often occur early, e.g., seizures, yet there is great variability in severity
- Anatomic hallmark is abnormal gyral development
- Because of temporal and causal reasons, often seen with abnormality of corpus callosum and/or septum pellucidum

Disorders of Migration

- In order of decreasing severity
  1) Schizencephaly
  2) Lissencephaly/Pachgyria
  3) Polymicrogyria
  4) Heterotopias – small collections not unusual incidental autopsy finding
Schizencephaly

- Usually described as open or closed lip, unilateral or bilateral, and by area (eg frontal, parietal, etc) More severe more likely associated with seizure, cognitive and motor delays

Lissencephaly

- Type I – Isolated (usually associated with chromosome 17 or x-linked) and Miller-Dieker syndrome
- Type II – Walker Warburg syndrome and Fukuyama congenital muscular dystrophy
Disorders Associates with Heterotopias

- X linked
- Metabolic – adrenoleukodystrophy, Menkes, Hurlers, Leighs
- Myotonic dystrophy
- Neurocutaneous – NF, TS, Itos
- MCA – SLO, Meckel Gruber, de Lange
- Chromosomonal – Trisomy 13, 18, 21
- Toxin exposure – CO, FAS

Organization

- Peak time – 5 mo to years postnatal
- Major events-
  1) Subplate neuron development
  2) Lamination or alignment, orientation, layering of cortical plate neurons
  3) Dendritic and axonal ramifications and synaptogenesis
  4) Programmed cell death - apoptosis
Disorders of Organization

- Mental retardation (idiopathic)
- Down syndrome
- Fragile X
- Angelman
- ? Autism
- Duchenne muscular dystrophy

Disorders of Organization - Potential Disturbance

- Prematures with PVL, ventilator dependence, decreased T4
- Poor nutrition
- Experiential deprivation
Myelination

- Peak time period: birth to years postnatal
- Considered as two phases, oligodendroglial proliferation, differentiation, and alignment followed by myelin deposition around axons

Myelination

- Five major general rules
  - 1) Proximal paths myelinate before distal
  - 2) Sensory paths myelinate before motor
  - 3) Projection paths myelinate before cerebral associative paths
  - 4) Central cerebral sites myelinate before cerebral poles
  - 5) Occipital poles myelinate before frontotemporal poles

Primary disorders of myelination

- Cerebral white matter hypoplasia
- Amino and organic acidopathies
- Hypothyroidism
- Postnatal undernutrition
- PVL
Intraventricular Hemorrhage

Grade based on CT at level of trigone
- I  Subependymal blood or < 10% of ventricle filled with blood
- II  10-50% of ventricle filled with blood
- III >50% of ventricle filled with blood
- IV Periventricular hemorrhagic infarction