Neuropathology and Pathogenesis of Perinatal Brain Injury

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Hypoxic-ischemic Brain Injury (HIE)

- Very important neurological problem of perinatal period
  - ✓Subsequent neurological deficits
    - Spasticity
    - Choreoatheotosis
    - Dystonia
    - Ataxia
  - ✓Large number
- In the premature
  - ✓Often accompanied by intraventricular hemorrhage

Neuropathology

- Vary with the
  - ✓Gestational age of the infant
  - ✓Nature of the insult
  - ✓Types of intervention

Major neuropathological varieties of neonatal hypoxic-ischemic encephalopathy
Selective neuronal necrosis
Parasagittal cerebral injury
Periventricular leukomalacia
Focal (/multifocal) ischemic brain necrosis, stroke

Selective Neuronal Necrosis

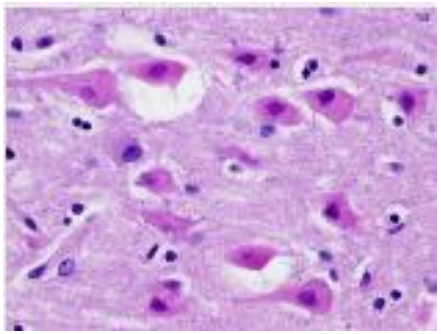
- Necrosis of neurons in a characteristic distribution
  - ✓Often widespread
  - ✓Often coexists with other manifestation of HIE
- Three basic patterns - clinical / imaging
  1. Diffuse ← very severe, very prolonged insult
     - Term and preterm
  2. Cerebral cortex-deep nuclear ← moderate to severe, prolonged
     - Term
  3. Deep nuclear ← severe, abrupt
     - Term
     - Preterm – pontosubicular, cerebellar injury

Cellular Aspect in Selective Neuronal Necrosis

- Neuron – primary site of injury
  - ✓Firstly, cytoplasmic vacuolation
    - Mitochondrial swelling
    - 5 – 30 minutes after the onset of hypoxia
  - ✓Differentiating oligodendroctyes – same sensitivity to glucose and oxygen starvation
  - ✓No structural alteration in astrocytes
  - ✓Least affect on microglia

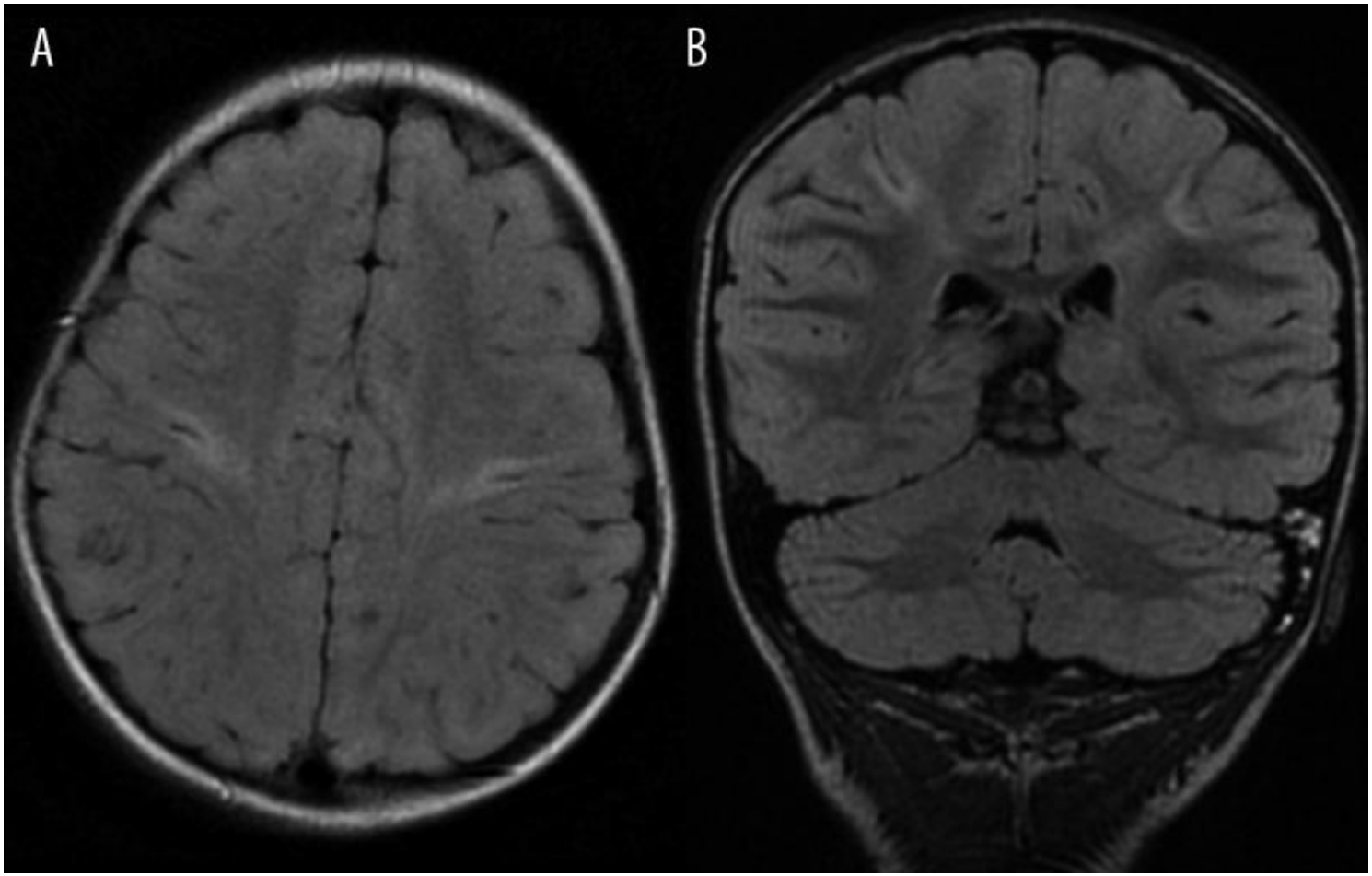
Cellular Aspect in Selective Neuronal Necrosis

- Temporal features



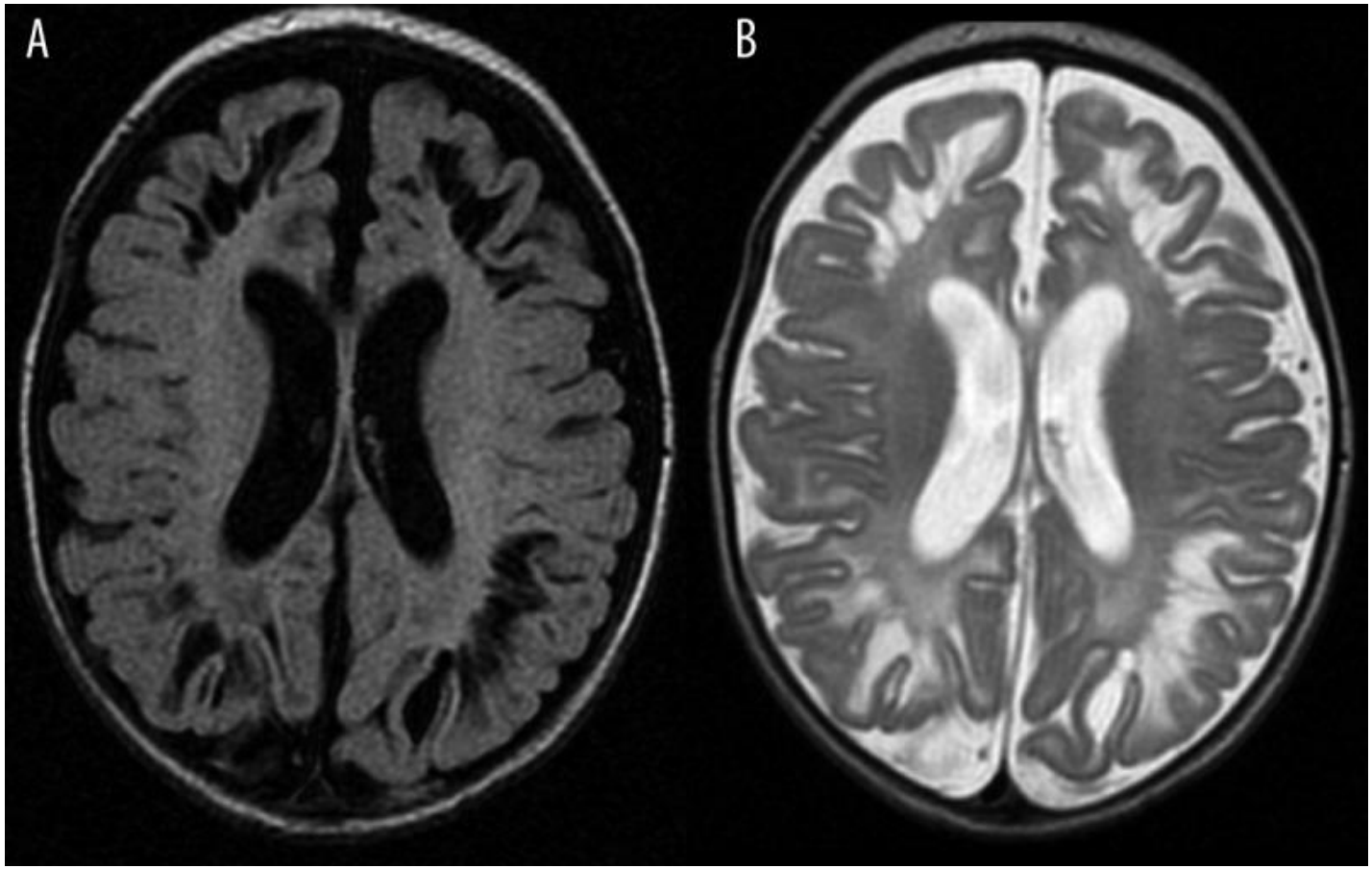
  - ✓Major changes seen by L.M after 24-36 hrs
    - Eosinophilia of neuronal cytoplasm
    - Loss of Nissl substance (endoplasmic reticulum)
    - Condensation or fragmentation of nuclei
    - Breakdown of nuclear and plasma membrane, swelling
  - ✓Several days after
    - Overt signs of necrosis
    - Appearance of microglial cells, by 3 – 5 days after the insult
    - Hypertrophic astrocytes
    - Foamy macrophages consume the necrotic debris
  - ✓Glial mat forms of the next several weeks
  - ✓Severe lesions, cavity formation, especially in cortex

Diffuse Neuronal Injury



Cerebral cortex and white matter injury in a term newborn after asphyxia. (**A**) FLAIR,ax; (**B**) CUBE/3D/FLAIR,cor.

Diffuse Neuronal Injury



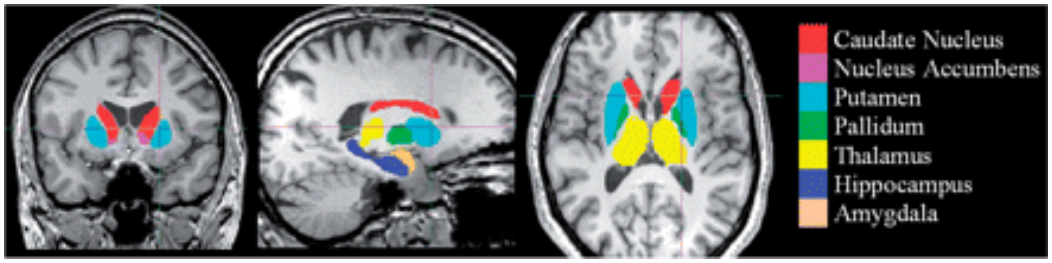
Multicystic encephalopathy in a 5-week-old child, visible despite therapeutic hypothermia. (**A**) FLAIR,ax; (**B**) FSE/T2,ax.

Diffuse Neuronal Injury

- **Cerebral cortex**
  - ✓Particularly vulnerable
    - Most – hippocampus (the premature – subiculum)
- Term infants
  - ✓The better differentiated neurons of calcarine, precentral, and postcentral cortices may be injured
  - ✓In very severe, diffuse cerebral cortex
  - ✓In deeper cortical layers, in depth of sulci, are especially affected
  - ✓More severe in border zones btw the major Cbr. a.
- Preterm infants
  - ✓Uncommon involvement of cortex ?- volume, gyrus

Diffuse Neuronal Injury

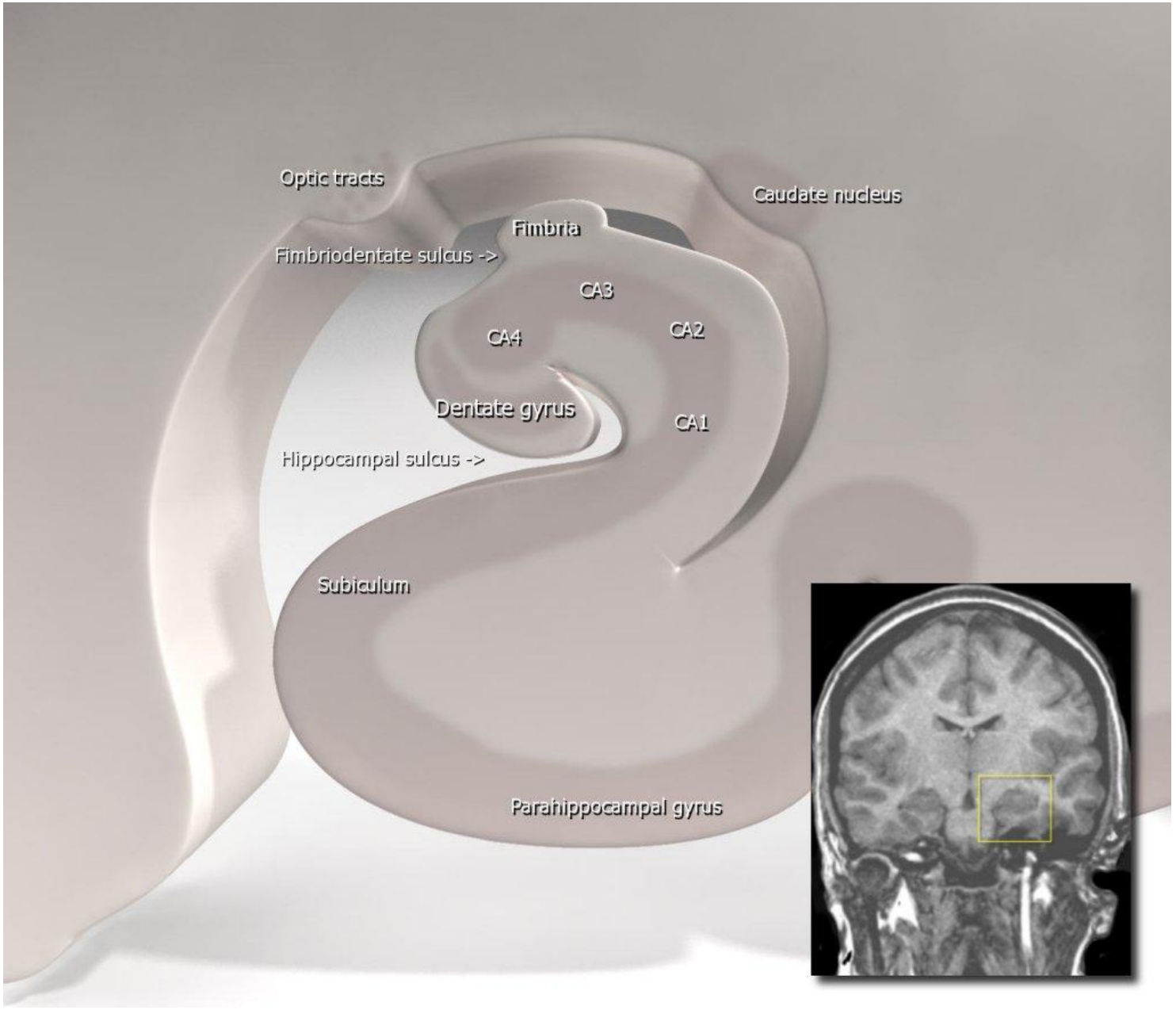
- **Deep nuclear structure**
  - ✓Thalamus and basal ganglia (BG)
    - Both preterm and term
- Term infants
  - ✓A particular pattern: combination of affection of thalamus, basal ganglia, and brain stem > cortex
  - ✓Hypothalamus, lateral geniculate – especially vulnerable
  - ✓More of putamen in BG



- Preterm infants
  - ✓Deep nuclear structure involvement – major form of gray matter injury (40 ~ 50%)
  - ✓More of globus pallidus in BG

Diffuse Neuronal Injury

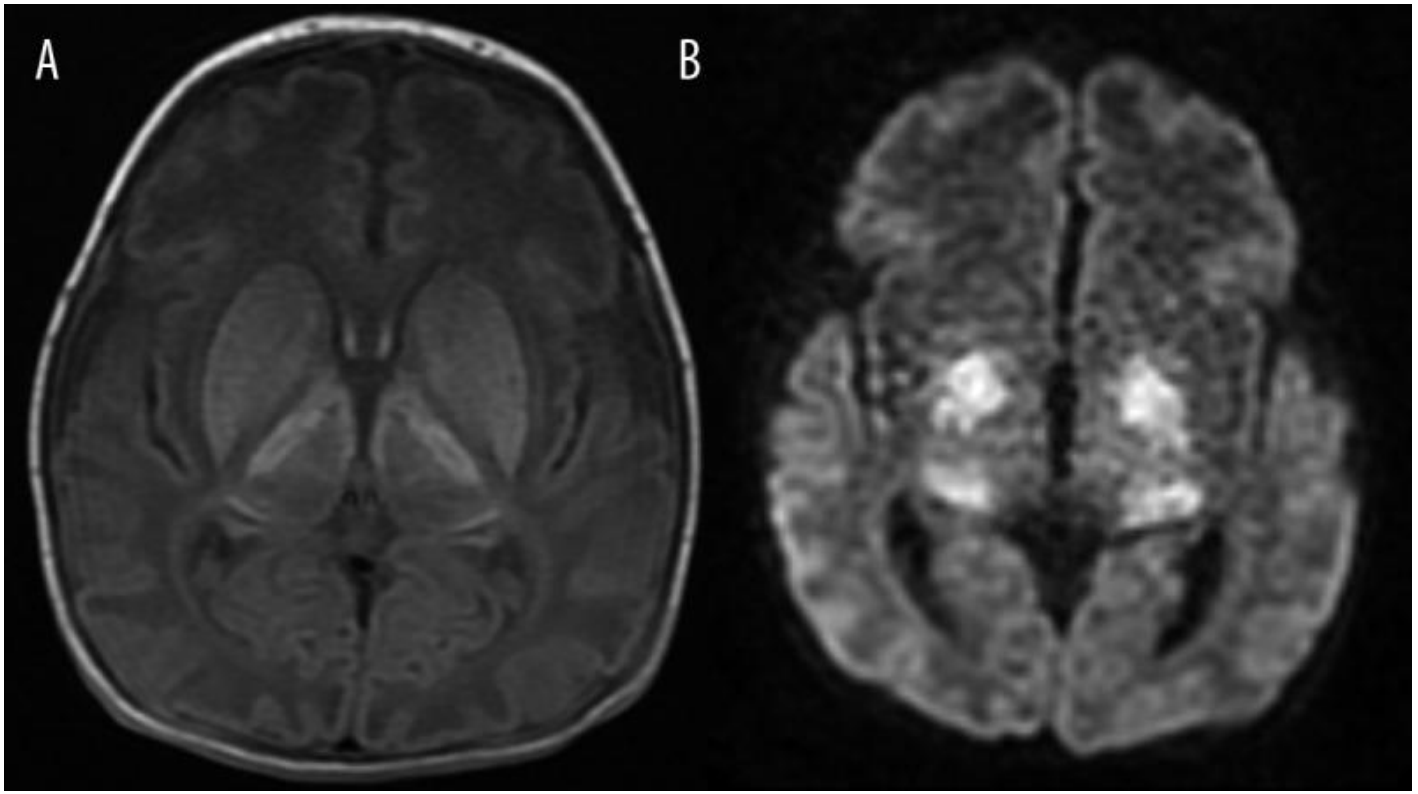
- **Brain stem**
  - ✓Particular characteristic in new born
  - ✓Combination with basal ganglia and thalamic involvement
- Term/Premature infants
  - ✓Term - Restricted to neurons
  - ✓Premature - Marked, result in cystic necrosis
- Location
  - ✓Midbrain - Inferior colliculus is most vulnerable, oculomotor and troclear nuclei, substantia nigra, R.F
  - ✓Pons – 5^{th} and 7^{th} C.N, R.F, dorsal cochlear nu.
  - ✓Pontosubicular neuronal necrosis (ventral pons)
  - ✓Medulla – dorsal nu. of vagus, nu.ambiguus(9^{th}, 10^{th} C.N), inferior olivary nu., cuneate and gracilis nu.


Optic tracts
Caudate nucleus
Fimbria
Fimbriodentate sulcus ->
CA3
CA4
CA2
Dentate gyrus
CA1
Hippocampal sulcus ->
Subiculum
Parahippocampal gyrus

Diffuse Neuronal Injury

- **Cerebellum**
  - ✓Especially vulnerable to HIE
  - ✓Purkinje cells in the term
  - ✓Granule cell in neurons in both term and premature
- Term infants
  - ✓Neurons of the vermis
  - ✓Subsequent disturbance of cerebellar growth
  - ✓Concomitant injury to thalamus and BG - postsynaptic
- Premature infants
  - ✓Neurons of dentate nucleus
  - ✓Cerebellar growth impair in very premature infants
- **Spinal Cord** – anterior horn cell, hypotonia

Cerebral-Deep Nuclear Neuronal Injury



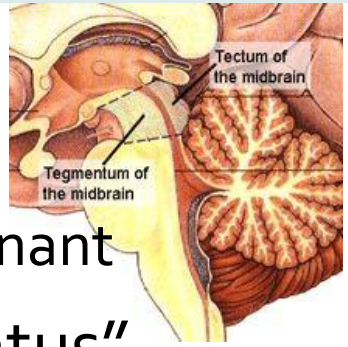
Injury of basal ganglia and thalamus in a term newborn – features of acute asphyxia. The lesions are hyperintense in all types of sequences (T1, T2, FLAIR) they show diffusion restriction. (**A**) SE/T1,ax; (**B**) DWI.

Cerebral-Deep Nuclear Neuronal Injury

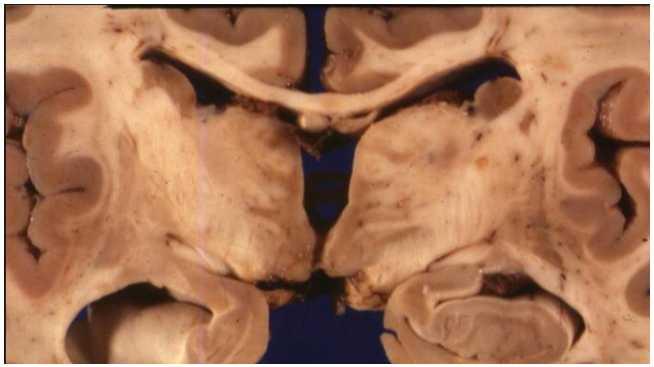
- Moderate-to-severe insult evolves in a gradual manner
- Among term infants, 35 ~ 85%
- Cerebral cortex: parasagittal areas of perirolandic cortex, hippocampus
- Basal ganglia (esp. putamen), thalamus

1. Deep nuclear-brain stem neuronal injury
2. Pontosubicular neuronal necrosis
3. Cerebellar injury

Deep Nuclear-Brain Stem Neuronal Injury



- Term infants
  - ✓Basal ganglia, thalamus, tegmentum - predominant
- Some cases may evolve to "Status marmoratus"
  - ✓Neuronal loss
  - ✓Gliosis
  - ✓Hypermyelination – putamen after 8 months (astrocyte)
  - ✓? Determinants of only gliosis *vs* atrophy



Pontosubicular Neuronal Necrosis

- One of selective neuronal injury with predominant involvement of neurons of
  - ✓Basis pontis (not tegmentum) and subiculum of hippocampus
  - ✓Least common
  - ✓Premature infant > 1~2 months beyond term
- Strong association with periventricular leukomalacia (PVL)
- Neuronal death in fascia dentata of hippocampus in 60%
- Basically apoptotic nature

Cerebellar Injury

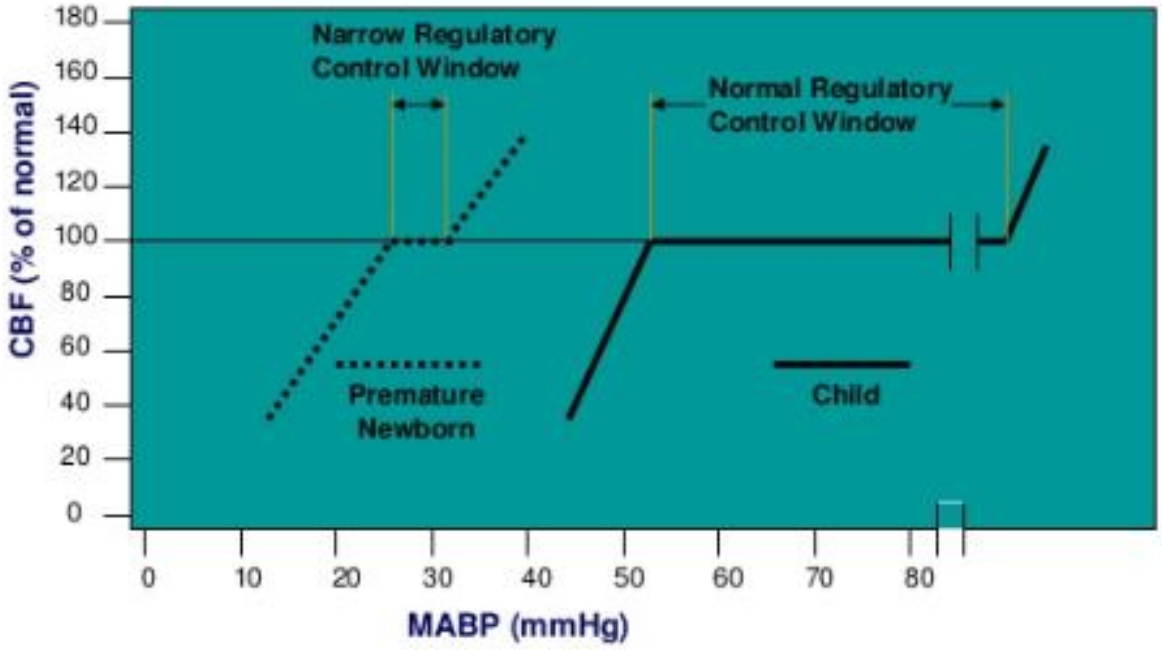
- Particularly characteristic of premature infants, esp. extremely low birth weights
- One of selective neuronal necrosis
- Occur
  - ✓Serious respiratory disease
- Bilateral, generally symmetric decreases of cerebellar hemispheric volumes
- Trophic (transsynaptic) relationship
  - ✓Strong association with cerebral white matter injury
  - ✓High frequency of brain stem cerebellar relay nu.

Pathogenesis of Selective Neuronal Necrosis

- Cerebral ischemia, impaired cerebrovascular autoregulation, and pressure-passive cerebral circulation
  - ✓Cerebral ischemia
  - ✓Deprivation of oxygen and glucose
  - ✓Followed by reperfusion and cascade of metabolic events
  - ✓Impaired autoregulation of CBF, affected by systemic hypotension
  - → Injury to certain vulnerable brain cell and regions
    - Neurons in the distribution of selective neuronal necrosis
    - Parasagittal cerebrum

Pathogenesis of Selective Neuronal Necrosis

CBF Autoregulation with Maturation



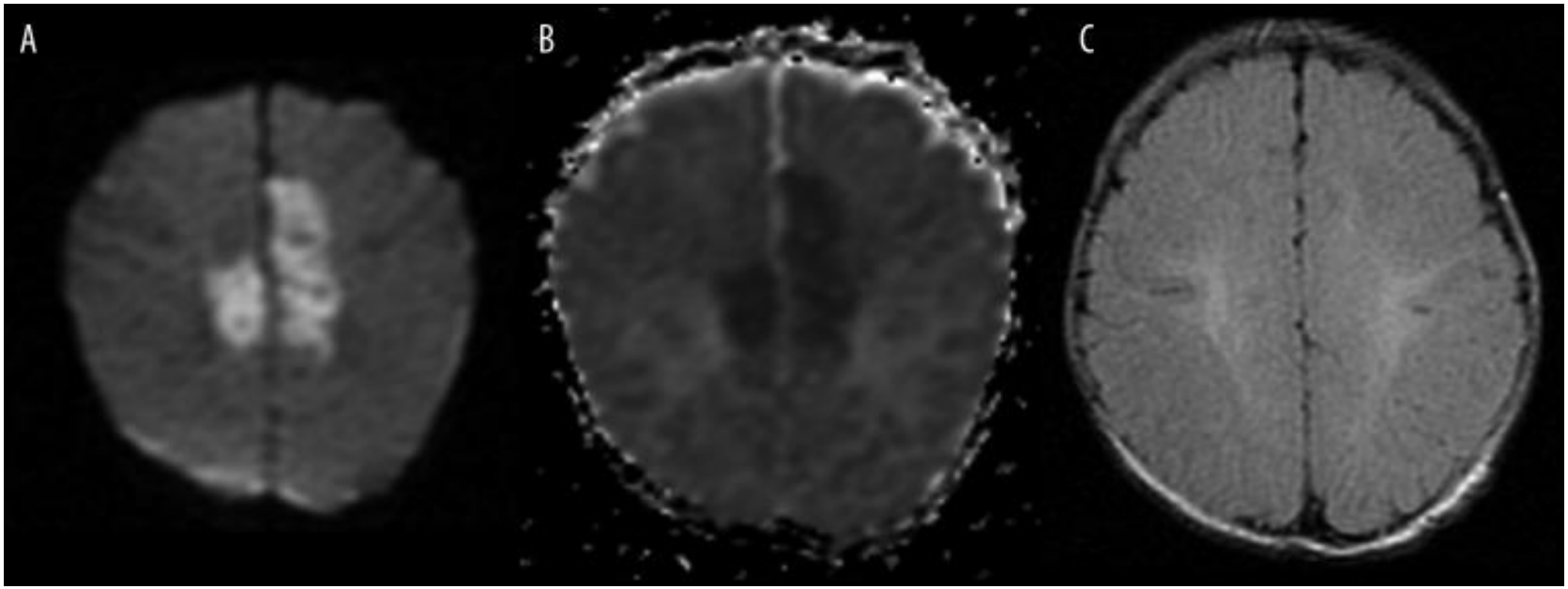
Pathogenesis of Selective Neuronal Necrosis

- Regional vascular factors
  - ✓Reason of selective vulnerability of neuronal groups
  - ✓Vascular border zones (depth of sulci, parasagittal cortex)
  - ✓Pontosubicular necrosis – hypocarbia and hyperoxemia
    - Cerebral vsoconstriction of premature infant
  - ✓Other factors also exist
    - Neuronal differentiation
- Regional metabolic factors
  - ✓Regional differences (proven in animal model)
    - anaerobic glycolytic capacity, energy requirements, lactate accumulation, mitochondrial function, calcium influx, nitric oxide synthesis, free radical formation, & scavenging capacity
    - Eg. High metabolic rate and energy use of deep grey matter

Pathogenesis of Selective Neuronal Necrosis

- Regional distribution of excitatory (Glutamate) receptors
  - ✓Mainly two receptors
    - N-methyl-D-aspartate (NMDA)
    - Alpha-amino-3-hydroxy-5-methyl-4-isoxasole-propionic acid (AMPA)
  - ✓Topography of HI neuronal death ≈ glutamate synapses
  - ✓Transient, maturation-dependent density of glutamate receptors
    - Eg. dense glutamergic innervation in basal ganglia in the perinatal period
  - ✓Extracellular glutamate increases dramatically at the receptors with HI
  - ✓Blockers of NMDA receptor-channel complex (also, calcium permeable AMPA receptor) can prevent HI neuronal death in vivo

Parasagittal Cerebral Injury



Acute, parasagittal brain injury, visible only in the DWI sequence. (**A**) DWI; (**B**) ADC; (**C**) FLAIR – undetectable lesions.

Parasagittal Cerebral Injury

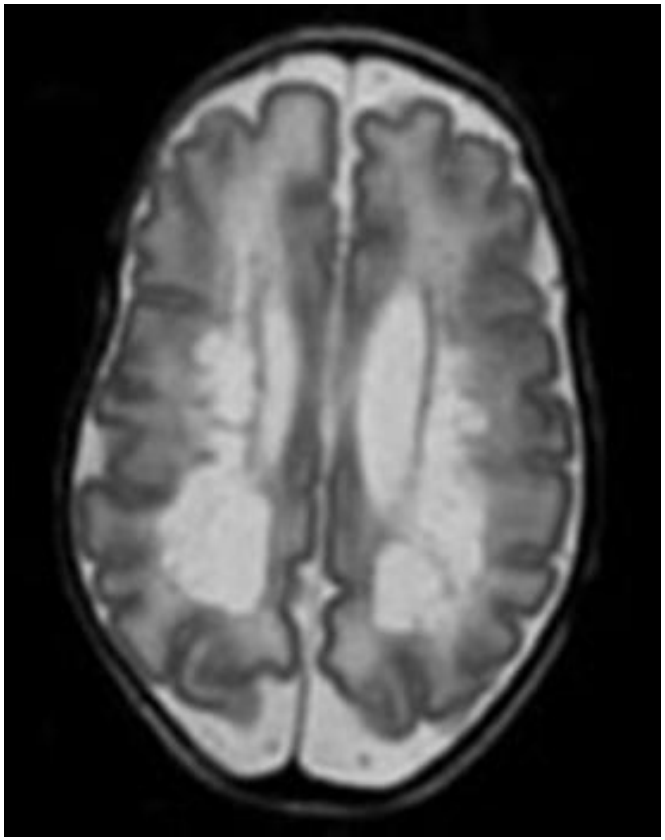
- Watershed infarct (45% of term infants with encephalopathy)
- A lesion of the cerebral cortex and subcortical white matter
  - ✓Parasagittal
  - ✓Superomedial aspects of the cerebral convexities
  - ✓Bilateral, usually symmetric

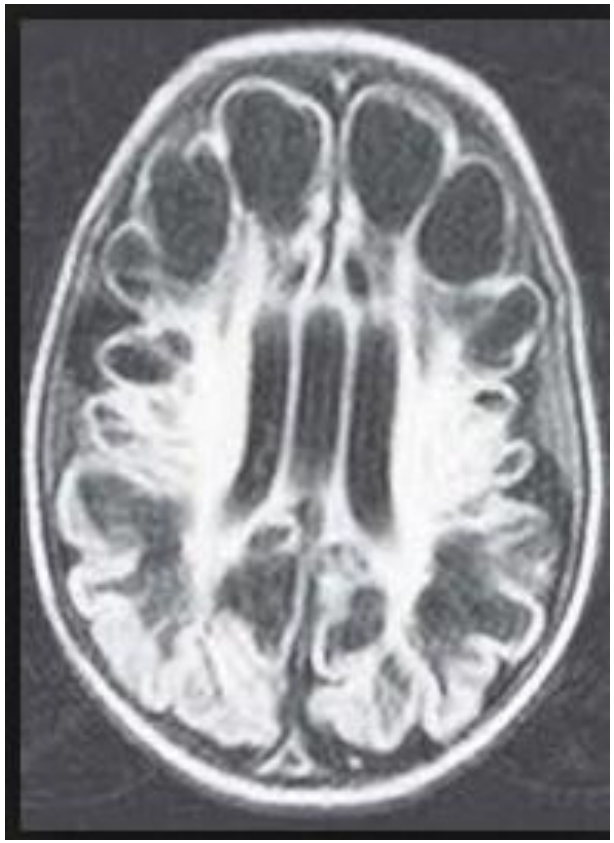
- Neuronal elements are most severely affected
  - ✓Usually nonhemorrhagic, infarction - may be hemorrhagic
- Posterior (Parieto-occipital) > Anterior
- Characteristic of the <u>full term with perinatal asphyxia</u>

Pathogenesis of Parasagittal Cerebral Injury

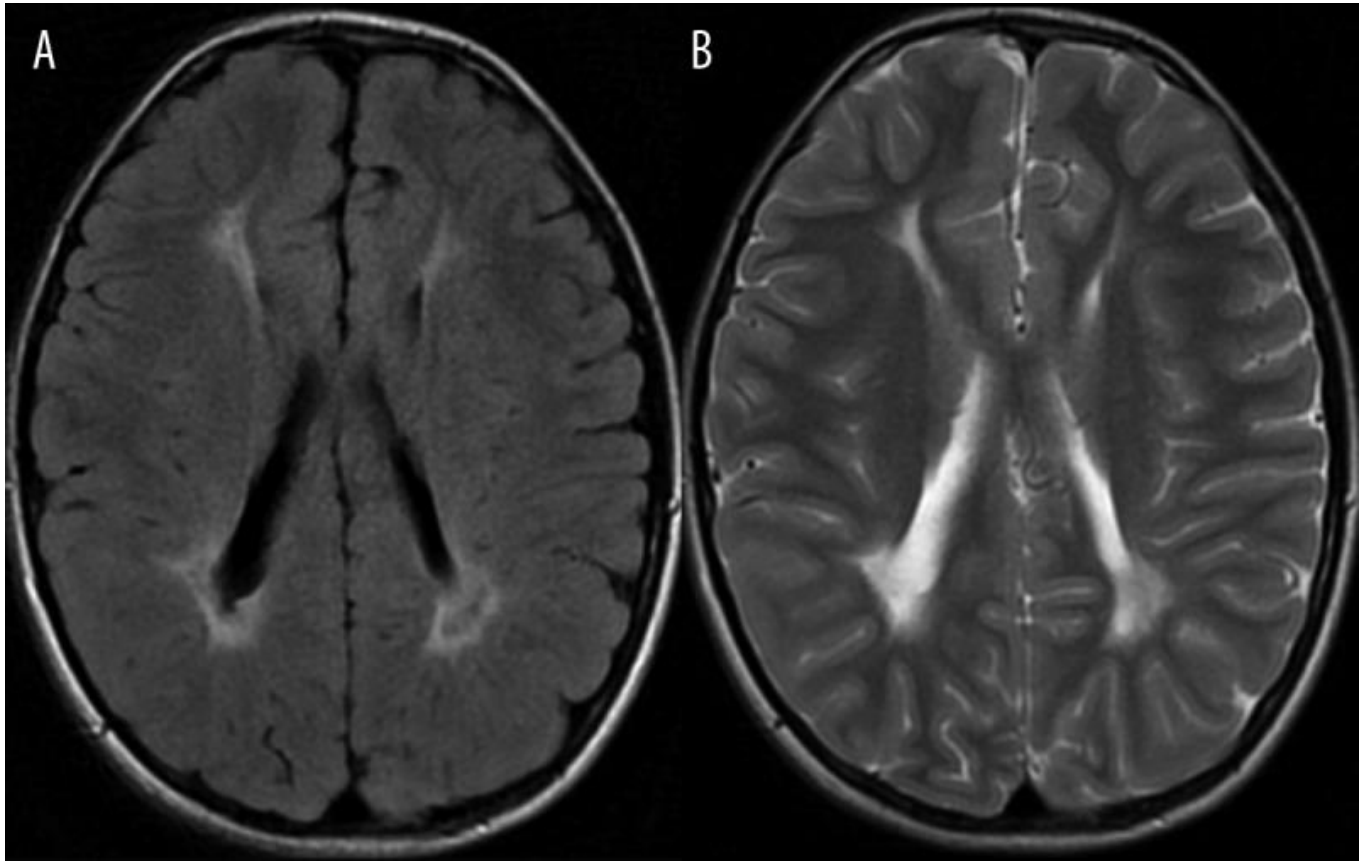
- Cerebral ischemia, impaired cerebrovascular autoregulation, and pressure-passive cerebral circulation
  - ✓Like selective neuronal necrosis
- Parasagittal vascular anatomical factors
  - ✓Areas of greatest ischemia
  - ✓Borderzones btw the end fields of the major Cbr. aa (proved by animal experiments)
    - Most susceptible to a fall in cerebral perfusion pressure
    - More marked injury in posterior cerebrum
- Vascular development appears to predispose the new born to ischemic injury to cortex & subcortex
    - Relatively avascular, triangular area at the depth of sulcus

Cystic Periventricular Leukomalacia





Noncystic Periventricular Leukomalacia



Bilateral, symmetrical paraventricular gliosis, uneven external outlines of the lateral ventricles, thinning of the white matter layer – classic pattern of hypoxic-ischemic lesions in a child born between 32 and 36 week of gestation. (**A**) FLAIR,ax; (**B**) FSE/T2,ax.

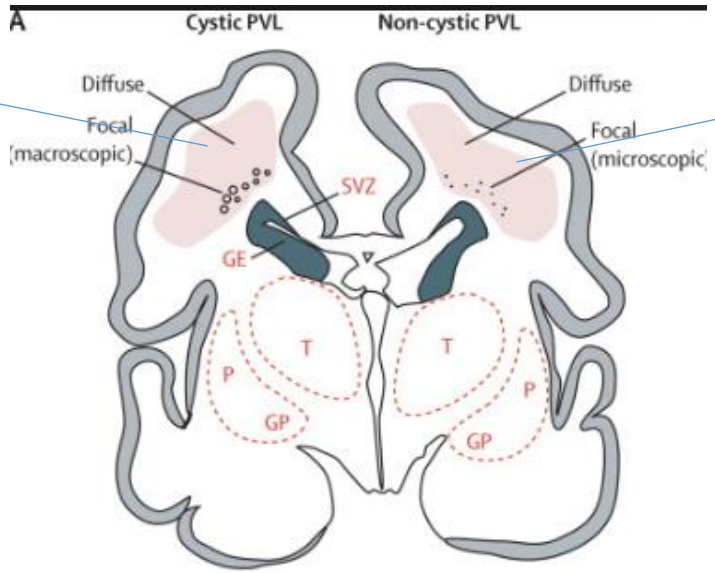
Periventricular Leukomalacia (PVL)

- Necrosis (softening) of white matter in a characteristic distribution
  - ✓White matter dorsal and lateral to the external angles of lateral ventricles
  - ✓Less severe injury to the white matter peripheral to these focal necroses
- Two basic components
  - ✓Focal necrosis
    - With subsequent cyst formation or glial scarring
    - Basic nomenclature
  - ✓More diffuse gliosis
    - Involving both astrocytes and microglia

Periventricular Leukomalacia

- Cystic PVL
  - ✓Classic lesion
  - ✓Necrotic component is macroscopic → cystic formation
- Non cystic PVL
  - ✓More common concurrent lesion
  - ✓Microscopic necrosis → small glial scar, rather than a cyst

↓Pre-oligos
+ Astrogliosis



↓Pre-oligos
+ Astrogliosis

Periventricular Leukomalacia

- Diffuse gliosis surrounding and peripheral to the necrosis, both types
- Many premature infants – diffuse white matter gliosis alone without focal necrosis
  - ✓ Difficult to classify
  - ✓ Mildest end of a continuum of white matter disease
- Incidence (autopsy)
  - ✓ Vary: ≈ 25 ~ 80%

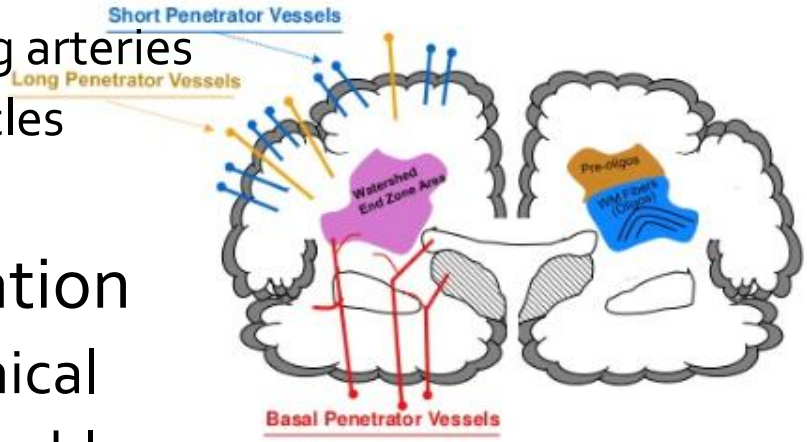
1) In premature infants
2) Postnatal survival of more than a few days
3) Having intraventricular hemorrhage
4) Evidence of cardiorespiratory disturbances
5) Evidence of antenatal maternal-placental-fetal infection

Periventricular Leukomalacia

- PVL is not uncommon in term infants
- Incidence of noncystic PVL is difficult to establish
  - ✓Below the resolution of ultrasonography
  - ✓NICU care – high frequency of diffuse white matter abnormality
  - ✓Diffuse MRI signal abnormality
    - 21% at 1st week after birth in prematurity
    - 53% in next several weeks
    - 79% at term equivalents

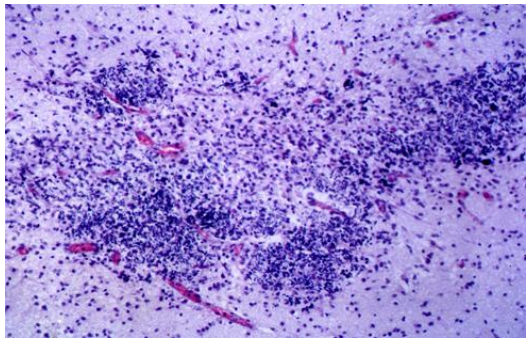
Cellular and Regional Aspects of PVL

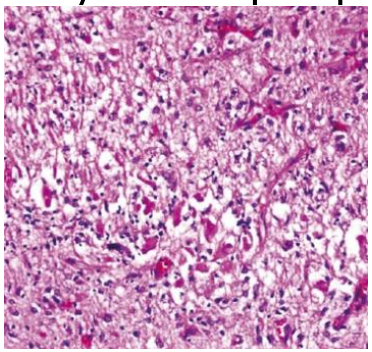
- Focal macroscopic periventricular necrosis + more diffuse white matter injury
  - ✓Focal necrotic lesion – deep in white matter
    - End zones of the long penetrating arteries
    - Near the trigone of lateral ventricles & around foramen of Monro
- Predilection for the lesion location
  - ✓Periventricular vascular anatomical factor & concentration of vulnerable pre-OLs
- Noncystic PVL, the focal lesion are likely not detected by ultrasonography during life



Cellular Aspects of PVL, at the focus

- First 6 ~ 12 hrs after acute HI insult at PV lesion
  - ✓ Loss of normal architecture and homogeneous periodic acid-Schiff (+) area of necrosis of all cellular elements
  - ✓ Round neuroaxonal swellings, especially at the periphery of the lesion



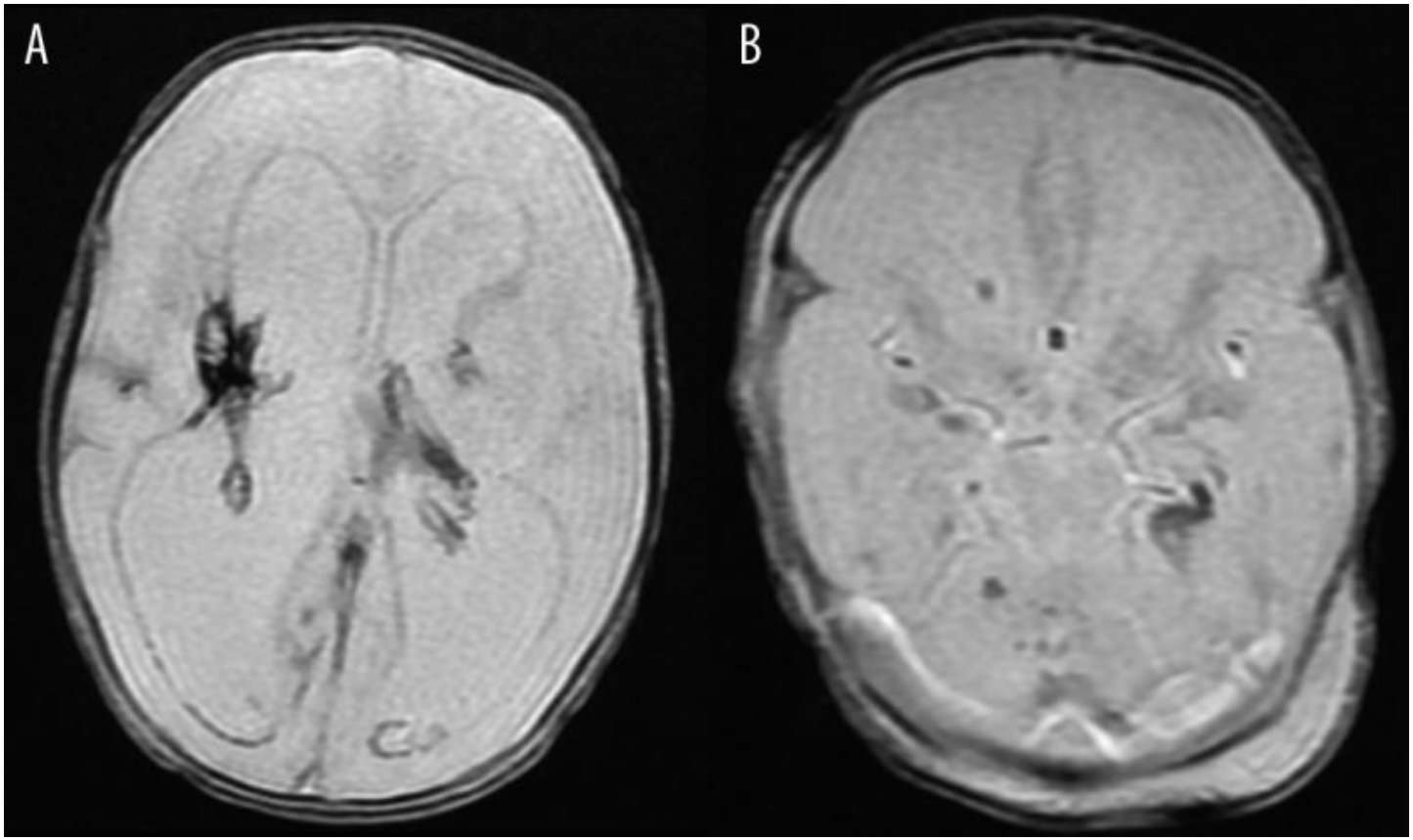


  - ✓ Axonal rupture → extravasation of glutamate
- Cellular Responses (cavity formation over 1~3 weeks)
  - ✓ Infiltration by microglia
  - ✓ Proliferation of hypertrophic astrocytes
  - ✓ Endothelial hyperplasia
  - ✓ Appearance of foamy macrophages

Cellular Responses of PVL, at the diffuse component

- Cellular Responses in cystic PVL
  - ✓ Pyknotic glial nuclei (acutely damaged)
  - ✓ Hypertrophic astrocytes
  - ✓ Not affect all cellular elements
- Early differentiating pre-OLs in cystic PVL
  - ✓ Hypomyelination and ventriculomegaly
  - ✓ Diminished cerebral white matter volume
  - ✓ Diminutions in pre-OLs
  - ✓ NMDA receptors (+): can lead to destruction
- Diffuse component in noncystic PVL
  - ✓ Injury is regionalized, vascular end zones
  - ✓ Preferential death of pre-OLs (by reactive oxygen/nitrogen species)
  - ✓ Marked prominence of astrocytes and activated microglia

Intraventricular or intraparenchymal hemorrhage



Intraventricular or intraparenchymal hemorrhage resulting from hypoxic-ischemic event in two different neonates born before 32 week of gestation. GRE/T2*,ax. (**A**) within supratentorial compartment; (**B**) infratentorial.

Hemorrhage in PVL

- Not uncommon, occasionally serious
  - ✓25% of PVL infarcts, post-morterm
  - ✓Most, petechial and circumscribed
  - ✓May be massive, difficult to distinguish from PV hemorrhagic venous infarction (severe IVH)
- Potential role of iron in the generation of ROS

Neuropathological Sequelae

- Large focal periventricular lesions
- Tissue dissolution after 1 ~ 3weeks
- Multiple small cavities
  - ✓With gliosis, these cavities usually constrict
  - ✓Some may no longer visible
- Subsequently,
  - ✓Deficient myelin
  - ✓Focal ventricular dilation – region of trigon of lat. Vt.
- Diffuse involvement of white matter, deficient myelin → diffuse ventricular dilation

Gray Matter Disease in PVL

- Gray matter is common and important accompaniment
  - ✓Reduction (≈30%) in cortical gray matter of PVL at term
  - ✓Possibility of disturbance of cortical development in the absence of major white matter abnormality
    - Especially parieto-occipital cortex
    - Deep nuclear structure volume was decreased (most immature infants, not only with white matter injury)
- MRI study for children and adults - premature
  - ✓Decreased cortical / deep nuclear gray matter volumes
  - ✓Abnormalities of cortical thickness and fiber tracts
    - Sensori-motor
    - Parieto-occipital, temporal, hippocampal cortices

Relationship of PVL to Neuronal Deficit

- Deep nuclear structures and cortex
  - ✓Destructive / Developmental
  - ✓Evidence of acute destruction - lacking
  - ✓However, neuronal loss and gliosis are common
    - Thalamus, basal ganglia
    - ½ of the infants
    - Direct effects or secondary trophic effects?
  - ✓(Marin-Padilla)
    - Alterations in morphology and organization of neurons and neuronal processes in cortex – cystic PVL
    - Weeks and months after the neonatal period
- Diminished cerebellar growth
  - ✓in premature + white matter injury

Relationship of PVL to Neuronal Deficit

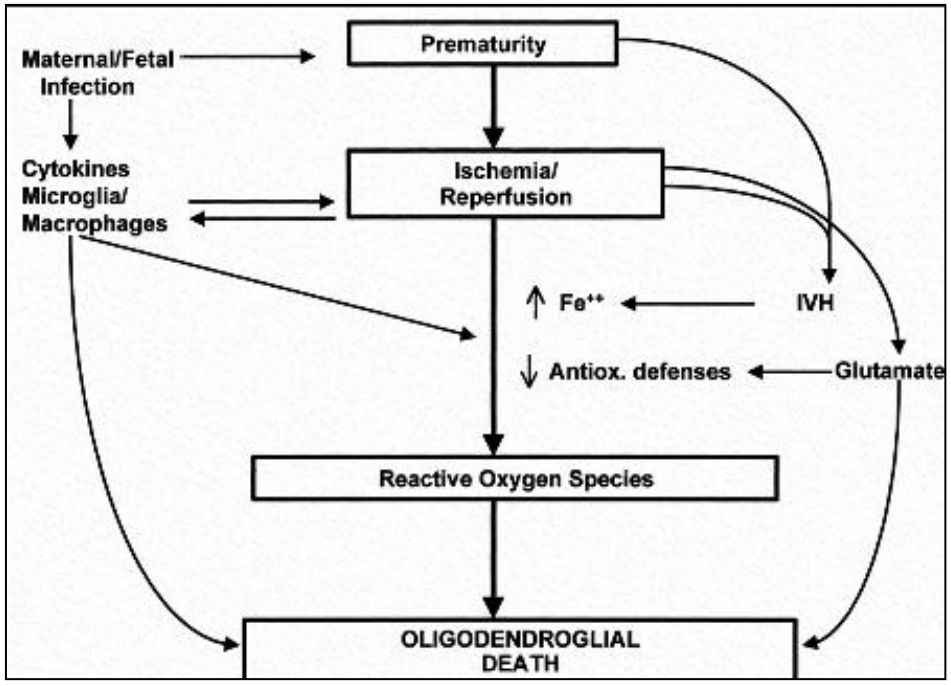
- Subplate neurons
  - ✓Crucial for cortical and thalamic neuronal development
  - ✓If injured, profound neuronal abnormalities
  - ✓Reach peak abundance during the premature period
    - Particularly vulnerable 22 ~ 34 weeks
  - ✓Transient sites for connections by awaiting afferents to developing cortex
    - Thalamocortical, corticocortical axonal projection
    - Guide axons to cortical and subcortical targets
    - Involve in structural and functional maturation

Relationship of PVL to Neuronal Deficit

- Axonal disturbances
  - ✓Profound impact on cortical and thalamic neuronal development
    - By retrograde and anterograde effects
  - ✓Pathologic findings
    - Axons are clearly detectable at 23 weeks, with immature markers:
    - GAP-43 (axonal growth and elongation) – high expression throughout the premature period (×4~5 fold than adult)
    - Immature axons are in very active development
  - ✓Immature axons are highly vulnerable to damage
  - ✓Axons are vulnerable to ischemia
  - ✓Oligodendroglial-axonal interactions (Pre-OLs)
    - Very critical for axonal survival, maturation, and function

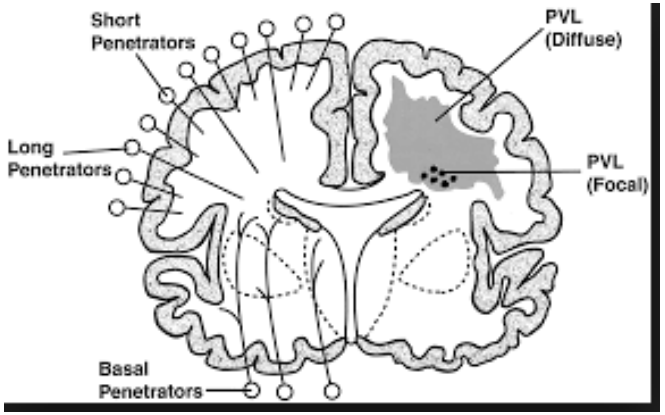
Pathogenesis of PVL

- Maturation dependent pathogenesis factors
- Two major upstream mechanisms
  - ✓Ischemia
  - ✓Infection / Inflammation



Ischemia in Pathogenesis of PVL

- Premature infants have propensity for Cbr.ischemia
  - ✓Especially to the white matter
  - ✓Presence of vascular end zones and border zones in WM
  - ✓Impairment of regulation of CBF
- Vascular anatomical and physiological factors
  - ✓Deep focal necrotic lesion – arterial end zones
    - Long penetrator – MCA
    - PVL: avascular necrosis
    - At 24~28 weeks of GA, long penetrator have few side branch & infrequent anastomoses with short penetrators
    - From 32 weeks, short penetrators develop, & anastomoses



Cerebral Ischemia, Impaired Autoregulation, and Pressure-passive Circulation

- Pressure-passive circulation
  - ✓In mechanically ventilated neonates, 53%
  - ✓Not markedly low BP, cumulative effect
    - Potentiation of excitotoxicity
    - Free radial accumulation
  - ✓Nearly all case of PVL were in the pressure-passive group
  - ✓Clinically stable premature infants seem less likely to exhibit apparent lack of cerebrovascular autoregulation
- Even in intact cerebrovascular autoregulation
  - ✓Marked cerebral vasoconstriction or severe systemic hypotension – impaired CBF to the cerebral vascular end zones and border zones
    - ✓Hypocarbia or hypotension $\propto$ PVL
    - ✓Impaired CBF $\propto$ PVL occurrence

Infection/Inflammation in Pathogenesis of PVL

- Maternal intrauterine infection
- Fetal systemic infection
- Clinical and epidemiological observations
  - ✓Maternal intrauterine infection causes a fetal systemic inflammatory response that results in injury to cerebral white matter
  - ✓Evidence: chorioamnionitis, funisitis, PROM
  - ✓Elevated levels of proinflammatory cytokines (IL-6, IL1β) in amniotic fluid or umbilical cord blood
  - ✓Intrauterine T-cell activation
- Postnatal infection and white matter injury
  - ✓Neonatal sepsis

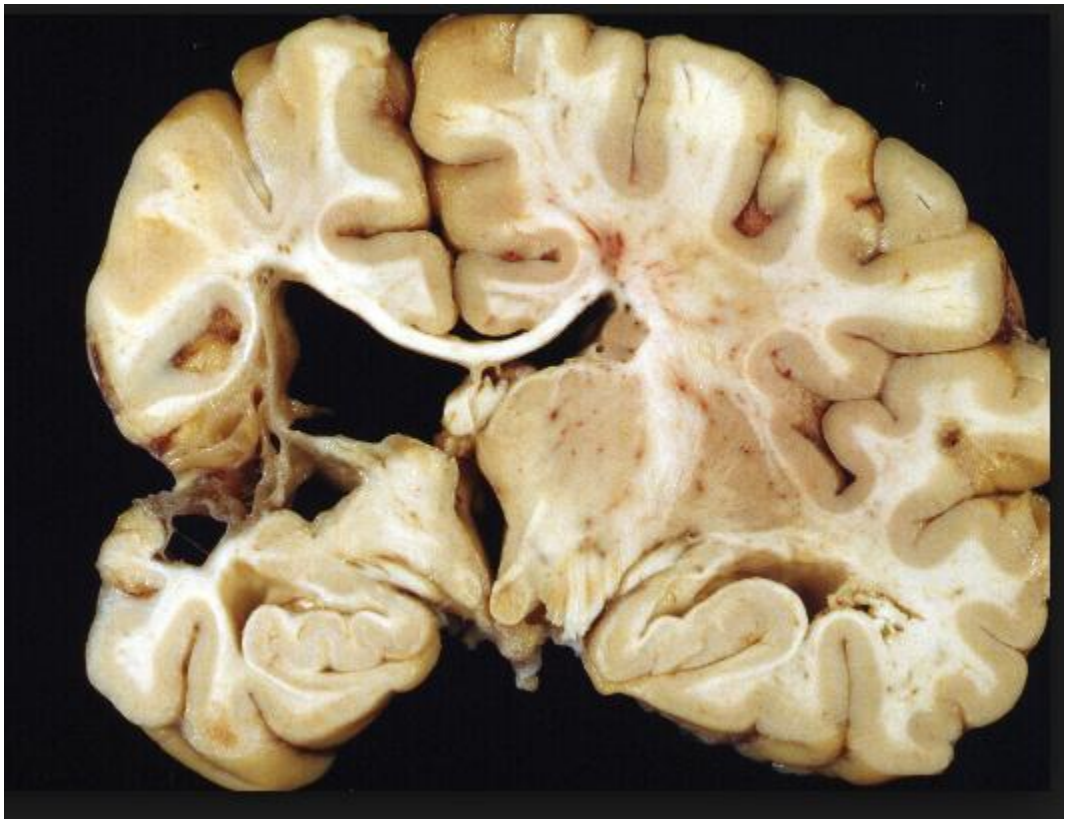
Infection/Inflammation in Pathogenesis of PVL

- Neuropathological observations
  - ✓In the diffuse component of PVL
    - Abundant IFN gamma in astrocytes
    - IFN gamma receptor was on pre-OLs (particularly toxic)
  - ✓Systemic cytokines or activated monocytic cells enter the brain through intact or damaged BBB

Central Role of Microglia in Pathogenesis of PVL

- Activated microglial cells secrete toxic diffusible products (ROS, RNS)
  - ✓More important the cytokines in white matter injury
- Role of microglia is clear
- ROS and RNS (Perhaps glutamate)
  - ✓Important in mediating the actions of these cells
- ROS/RNS toxicity and excitotoxicity are central
  - ✓to the intrinsic maturation-dependent vulnerability of pre-OLs to both hypoxia-ischemia and infection/inflammation
- Microglia
  - ✓Abundant in forebrain from 16~22weeks
  - ✓Concentrated in white matter, deep-to-superficial gradient

Focal Ischemic Brain Necroses



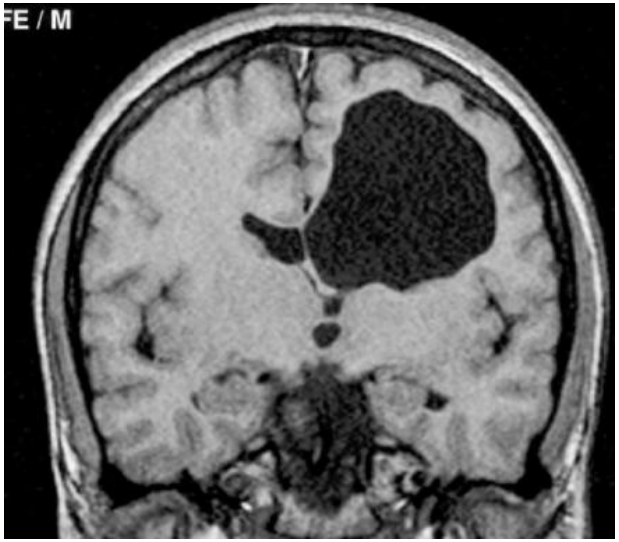
Middle cerebral artery infarct. In this case of focal, perinatal hypoxic ischemic damage, the patient has survived into later life.

Focal and Multifocal Ischemic Brain Necroses

- Within the distribution of single (or multiple) major cerebral vessel(s)
  - ✓Specific vascular distribution
  - ✓Arterial stroke
- Cellular aspects
  - ✓Necrosis of all cellular elements
    - After 18 ~ 24 hrs, observable by LM: anoxic neuronal change
    - ➢ Activated cells of monocyte-macrophage migrate from vessels
    - ➢ Foamy macrophage by 36 ~ 48 hrs
    - ➢ Astrocytic hypertrophy, 3~5 days
    - ➢ Dense mat of glial fibrillary processes
    - ➢ Mineralization of neurons, calcification, cavity formation
- Arterial distribution, 75% unilateral , 65% left a.

Venous thromboses

- 65% affect the frontal sagittal sinus
  - ✓Posterior portion
  - ✓50% Lateral sinus
- Infarction in 40 ~ 60%
  - ✓Brain edema
  - ✓Characteristically hemorrhagic
  - ✓IVH 20 ~35%



- Multifocal necroses and cavity formation
  - ≈ Porencephaly (unilateral, single)
  - ≈ Hydranencephaly (massive bilateral)
  - ≈ Multicystic encephalomalacia
- Any major destructive insult may result in cavity

Pathogenesis of Focal and Multi-focal Ischemic Brain Necroses

- Time of cavity formation
  - ✓2nd trimester ~ 1st postnatal weeks or months
  - ✓High water content
  - ✓Relative paucity of tightly packed myelinated fiber
  - ✓Deficient astrocytic response
- Major causes
  - ✓Difficult to determine whether intravascular occlusion or vascular maldevelopment
    - Prenatal stroke – vascular abnormalities (fetal imaging)
    - Genetic factors association with hydranencephaly, microangiopathy
    - Isoimmune thrombocytopenia
  - ✓Vasospasm - cocaine
  - ✓Vascular distortion by neck motion
  - ✓Arterial occlusion by embolus or thrombus

Pathogenesis of Focal and Multi-focal Ischemic Brain Necroses

- Sources of emboli
  - ✓Placental fragment: most common
  - ✓In fetal vessels (umbilical v.) – pass across foramen ovale
  - ✓Thrombi in internal carotid artery, portal vein, central venous catheter, cardiac sources
  - ✓More affect left hemisphere, predominantly MCA
- Thrombosis
  - ✓Artery or vein
    - Abnormality of the artery or vein per se
  - ✓Bacterial meningitis
  - ✓Trauma related vascular injury (intrauterine)
  - ✓Carotid artery dissection and fibromuscular dysplasia
  - ✓ECMO, Abnormal blood volume and coagulability, DIC

Pathogenesis of Focal and Multi-focal Ischemic Brain Necroses

- Hypercoagulability
  - ✓Polycythemia
  - ✓Endogenous factors
    - Extreme importance
    - Factor V Leiden mutation (resistance to activated protein C)
    - Prothrombin mutation
    - MTHFR deficiency (hyperhomocysteinemia)
    - Protein C deficiency – purpura fulminans
    - Protein S deficiency - purpura fulminans
    - Antithrombin III deficiency
    - Antiphospholipid antibody
    - Elevated lipoportein α
    - Elevated factor $VIII_c$
  - ✓Usually combined with other factors
    - Chorioamnionitis, sepsis, congenital heart disease, twin

Main References

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Thank you for your attention.