NEUROPATHOLOGY & PATHOGENESIS OF CEREBRAL PALSY

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대한소아재활 발달의학회 연수강좌. 2018.11. 10

Cerebral palsy (CP)

- Definition
  - a **static lesion** occurring in the **immature brain** that leaves children with a **permanent motor impairment**
  - The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior, by epilepsy, and by secondary musculoskeletal problems.

Cerebral palsy, Miller Fisher 2002
Physical Medicine and Rehabilitation, Braddom, 5th edition

CP, Epidemiology

- **Prevalence**
  - 2-2.5 per 1000 liver births
  - Changed very little over the past 40 years, despite treatment advances
    - ↑ incidence from survivors of NICU
    - ↑ very low birth weight & very early gestation
    - ↑ Multiple births, ↑ maternal age

- **Patterns of CP**
  - ↑ diplegia & spastic quadriplegia
  - ↓ hemiplegia & athetosis

Risk factors of CP

- Prenatal factor : >75%
- **Most important** factor : **prematurity** (GA <37wk)

Table 47-1 Risk Factors Associated with Cerebral Palsy

Preconception	Antenatal	Intrapartum	Neonatal	Postnatal
Maternal seizures	Birth defects	Birth hypoxia	Seizures	Stroke
Intellectual disability	Small for gestational age	Meconium staining	Respiratory distress	Abusive head trauma
Thyroid disease (hyper or hypo)	Low birth weight	Meconium aspiration	Hypoglycemia	Bacterial meningitis
History of stillbirth or neonatal death	Placental abnormalities	Abnormal duration of labor	Infections	Motor vehicle crashes[10]
Maternal age >40 years	Maternal disease during pregnancy (respiratory, heart, seizures, incompetent cervix)	Fetal presentation[34]	Jaundice[34]	
Low socioeconomic status[34]	Abnormalities in fluid volume			
	Maternal bleeding in 2nd and 3rd trimesters			
	Hypertension			
	Preeclampsia			
	Chorioamnionitis[34]			

Physical Medicine and Rehabilitation, Braddom, 5th edition

Perinatal Brain Injury, Neuropathology

1. **Hypoxic-ischemic encephalopathy (HIE)**

2. **Germinal matrix-intraventricular hemorrhage (GMH-IVH)**

3. **Bilirubin encephalopathy**

Hypoxic-Ischemic Encephalopathy

- brain injury caused by the combination of inadequate blood flow and oxygen delivery to the brain

- *acute intrapartum event sufficient to cause neuronal injury evidenced by (AAP and ACOG) :*
  - Metabolic acidosis (pH <7.0 and base deficit ≥12) in fetal umbilical cord arterial blood ,
  - Need for respiratory support also starting in the first minutes,
  - Low Apgar scores longer than 5 minutes.
  - Neonatal neurologic sequelae (eg, seizures, coma, hypotonia)
  - Multiorgan failure (eg, kidney, lungs, liver, heart, intestines)

HIE - Etiology

ANTEPARTUM	**MATERNAL RİSK FACTORS**	**FETAL RİSK FACTORS**
	– Endocrine diseases (diabetes vs) – Hypertension, Cardiovascular diseases – Epilepsia – Preeclampsia – Drug addiction – Drugs(lityum, MgSO4, reserpine) – Last trimester bleeding, Profound anemia – Mothers age (>35 years) – Multiparity, Severe infections	– Twins, triplets – Postmaturity – Prematurity – İntrauterin growth retardation – Congenital anomalies – Fetal infections – Fetal anemia – Fetal dystrithmias
İNTRAPARTUM	**PLACENTA AND CORD**	**OTHER RISK FACTORS**
	– Ablatio placenta – Placenta previa – Small placenta – Prolapsus of umbilical cord – Tight nuchal cord – Cord anomalies – Umbilical vein/arterial anomalies	– Abnormal presentations – Cesarian section – Vacuum/Forceps application – Premature rupture of membranes – Meconium stained amniotic fluid – Accelerated birth (<30 min) – Prolonged birth (>2 hrs) – Birth induction – Sedatives use
POSTPARTUM	**RISK FACTORS**	
	– Serious pulmonary diseases (Meconium aspiration, RDS, Pneumonia) – Congenital heart diseases – Sepsis and shock – Recurrent apnea – Serious congenital anomalies – Neuromusculary diseases – Prematurity – Severe anemia – Cardiovascular collaps (sepsis, severe blood loss, adrenal hemorrhage)	

HIE - Pathophysiology

- ***Cerebral injury and neuronal death***
- The underlying pathophysiology of perinatal HIE is difficult to study in the human, thus the neonatal rat model for HI brain injury has been developed to model this human condition.
- Much of what we know is derived from studies conducted in animal models.

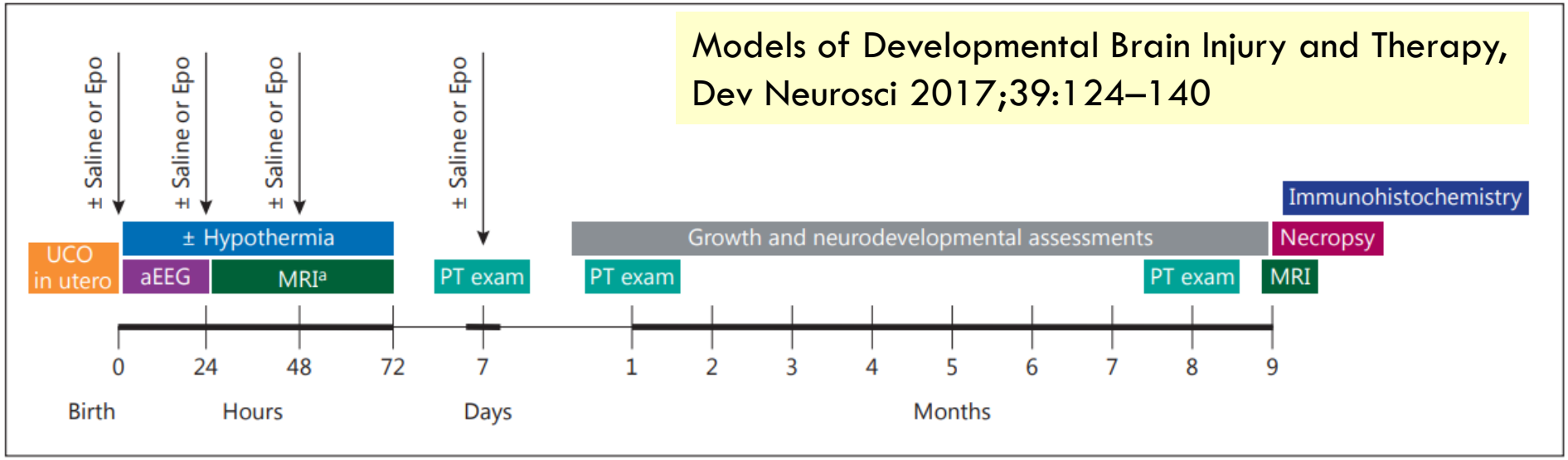
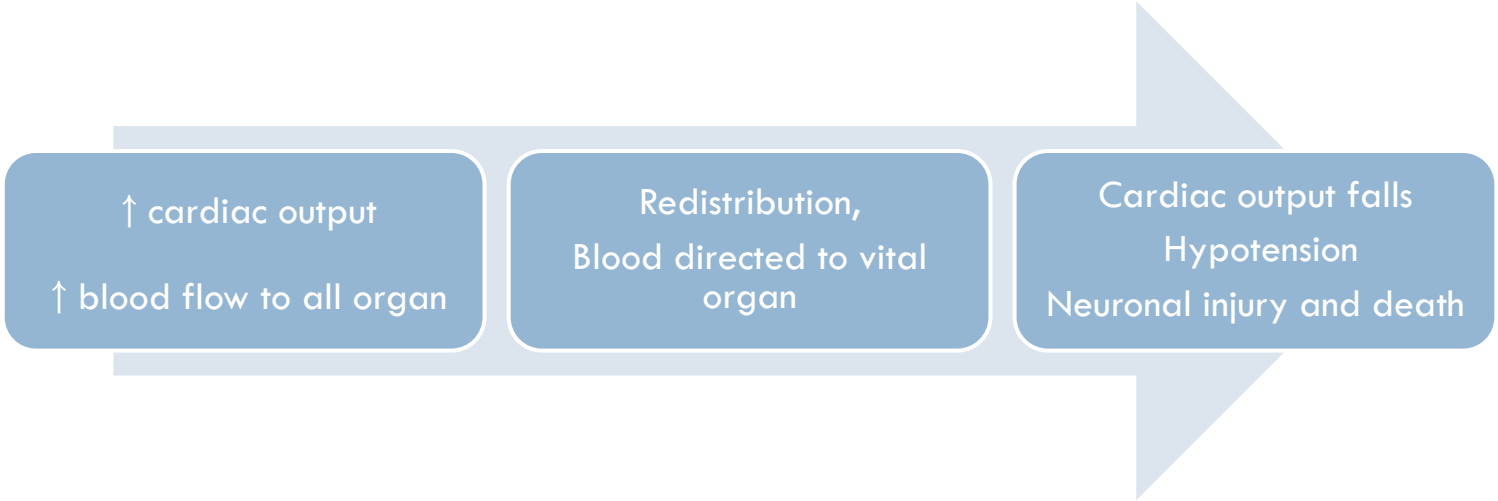
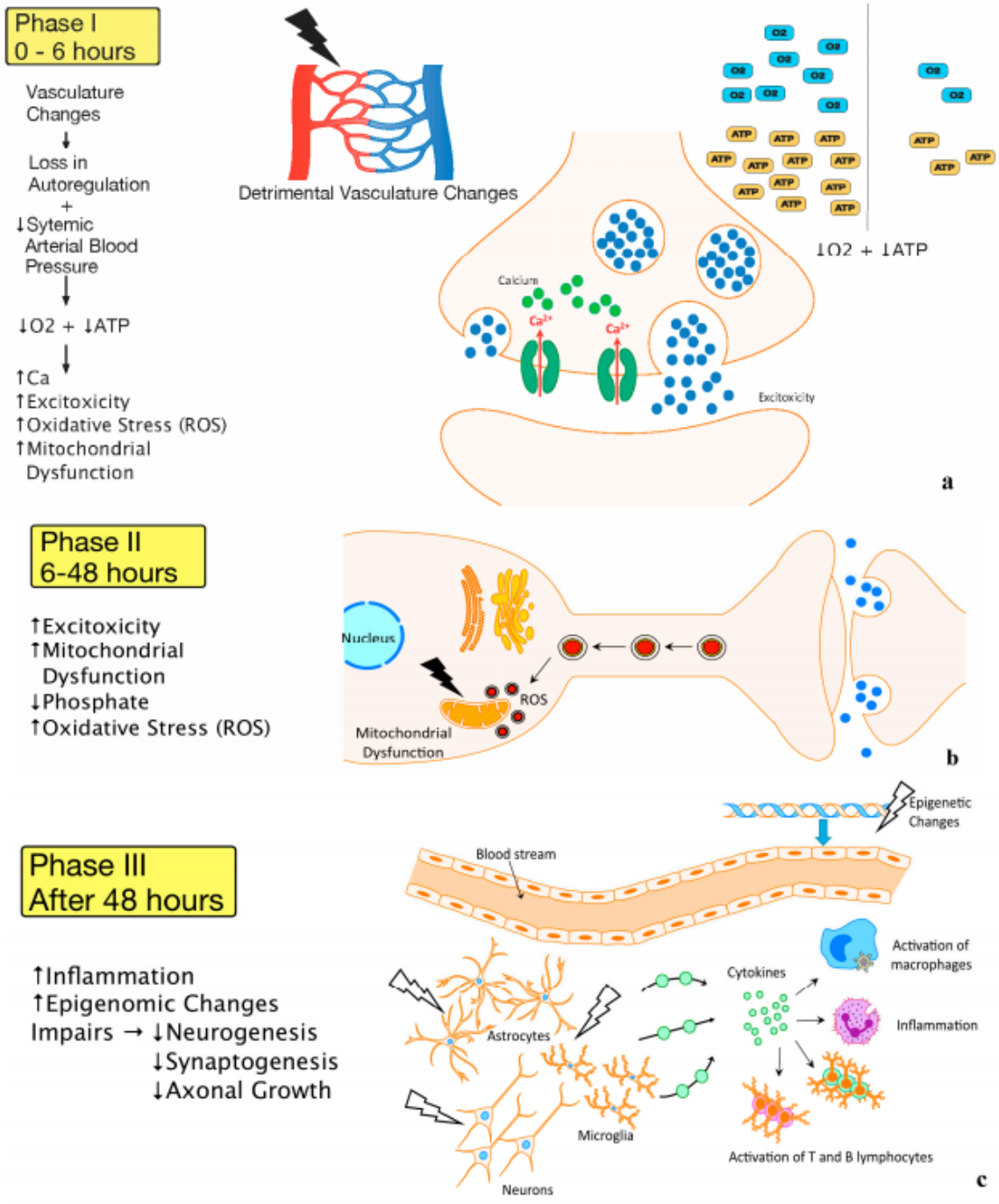


Fig. 1. An overview of the procedures and assessments for the non-human primate model of perinatal asphyxia. UCO, umbilical-cord occlusion; Epo, erythropoietin; aEEG, amplitude-integrated electroencephalography; MRI, magnetic resonance imaging (and diffusion tensor imaging); PT, physical therapy. [a] The first MRI scan was performed at either 24 or 72 h of age.

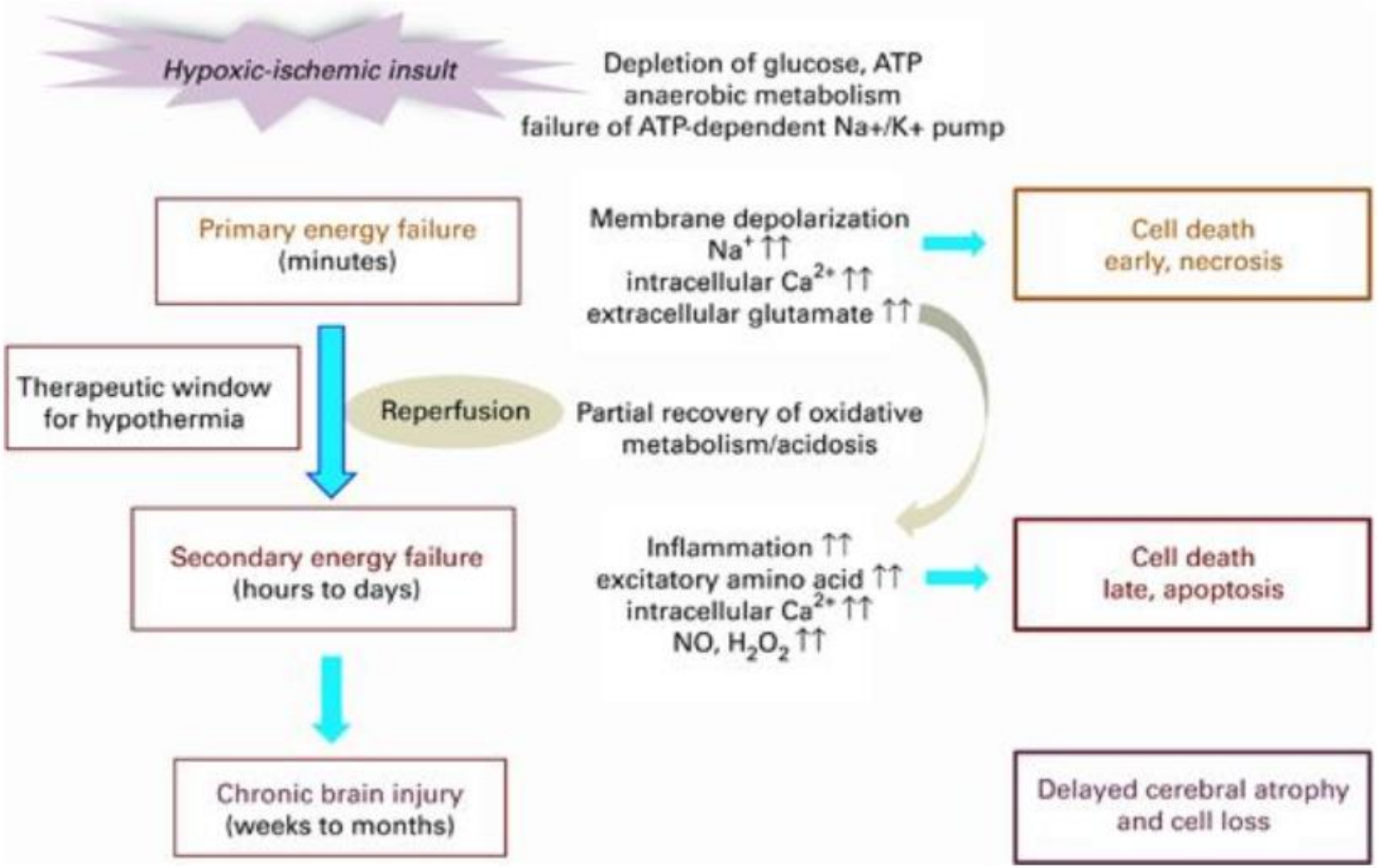
Hypoxic-ischemic insult

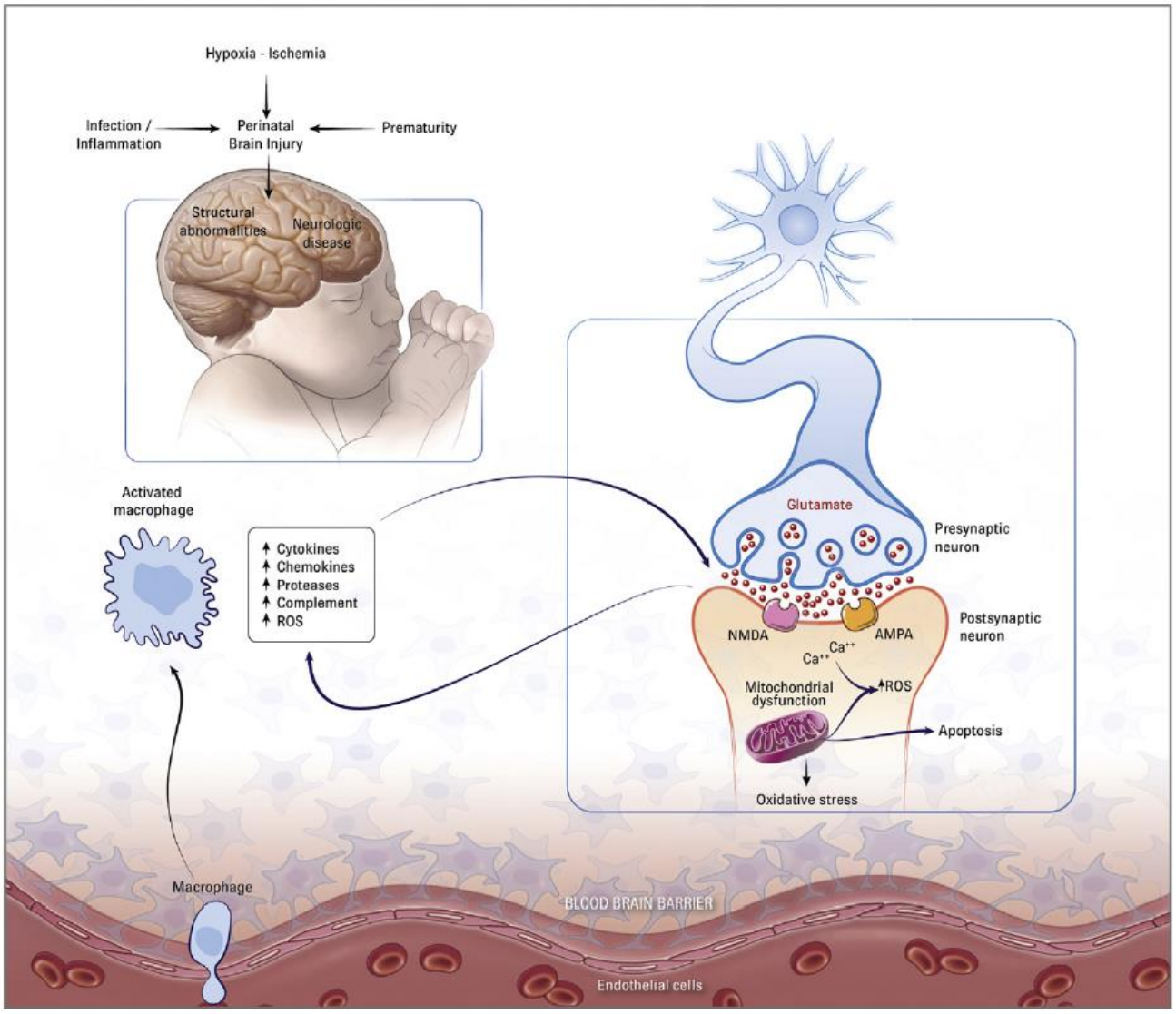


- Figure 2. (a) Vasculature Changes and Primary Energy Failure (Phase I) Legend: A visual representation of the first phase of HIE. Detrimental changes to the vasculature following an HIE insult lead to loss of autoregulation and severe lowering of the systemic arterial blood pressure. This causes a decrease in oxygen, depletion of ATP, as well as increases in excitotoxicity, intracellular calcium, oxidative stress, and mitochondrial dysfunction; (b) Secondary Energy Failure (Phase II). Legend: A schematic representation of the second phase of HIE reveals continued excitotoxicity, oxidative stress, and mitochondrial dysfunction; (c) Chronic Inflammation (Phase III). A pictorial representation of the third phase of HIE shows injury to microglia, neurons, and astrocytes leads to continuous release of cytokines and other detrimental factors causing chronic inflammation which in turn leads to epigenetic changes, as well as impairments of synaptogenesis, axonal growth, and neurogenesis.



- Neuroprotective Strategies after Neonatal Hypoxic Ischemic Encephalopathy, Int. J. Mol. Sci. 2015,


Hypoxic-ischemic insult
Depletion of glucose, ATP
anaerobic metabolism
failure of ATP-dependent Na+/K+ pump
Primary energy failure
(minutes)
Membrane depolarization
Na^+ ↑↑
intracellular Ca^{2+} ↑↑
extracellular glutamate ↑↑
Cell death
early, necrosis
Therapeutic window
for hypothermia
Reperfusion
Partial recovery of oxidative
metabolism/acidosis
Secondary energy failure
(hours to days)
Inflammation ↑↑
excitatory amino acid ↑↑
intracellular Ca^{2+} ↑↑
NO, H_2O_2 ↑↑
Cell death
late, apoptosis
Chronic brain injury
(weeks to months)
Delayed cerebral atrophy
and cell loss



The effects of hypoxia–ischemia, inflammation, and prematurity on the fetal brain may lead to a common pathway of perinatal brain injury marked by neuronal excitotoxicity, mitochondrial impairment with cellular apoptosis and generation of reactive oxygen species (ROS), and inflammation induced by microglial activation. AMPA, a-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; NMDA, N-methyl-D-aspartate.

Novak CM, Ozen, M, Burd I: Perinatal Brain Injury: Mechanisms, Prevention, and Outcomes, Clin Perinatol 45 (2018) 357–375

HIE - Neuropathology

A. Selective neuronal necrosis

B. Parasagittal cerebral injury

C. Periventricular leukomalacia

D. Focal and multifocal ischemic brain necrosis

A. Selective neuronal necrosis

- Most common pattern of HIE
- Necrosis of neurons in a characteristic distribution
  - Common involvement of Neuron in

    cerebral cortex, basal ganglia,

    thalamus, brain stem (esp. midbrain, pons)
    - ↑ excitatory Glutamate receptors

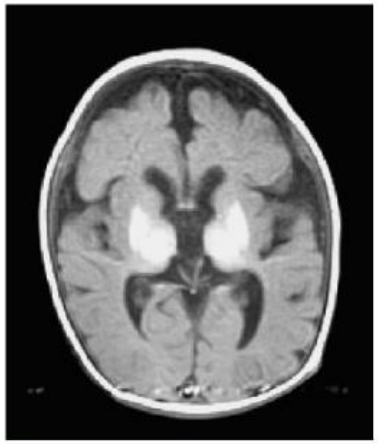


그림 16-1 저산소성-허혈성 손상에 의한 양측 기저핵과 시상의 선택적 신경원 괴사를 보이는 뇌자기공명촬영 소견(생후 5개월 남아).

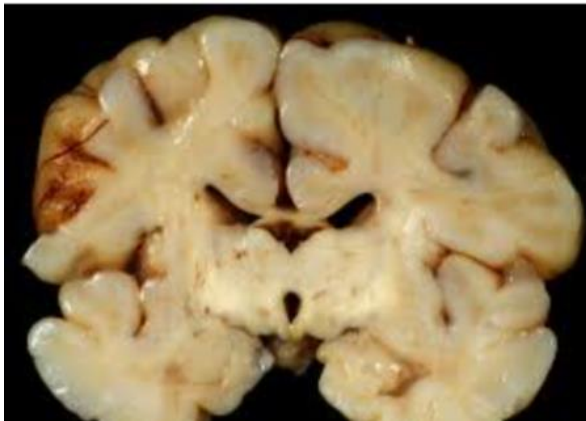
- Reason of **selective vulnerability** of neuronal groups
  - Neuron, Oligodendrocyte, astrocyte, microglia

    More vulnerable to ischemia
  - Hippocampal pyramidal cells of CA1, pyramidal neocortical neurons (layers 3,5 and 6), Purkinje cells, striatal neurons

A. Selective neuronal necrosis

- Symptoms
  - Depending on the function of damaged neurons
  - Most, developing cognitive dysfunction
  - Involvement of thalamus & basal ganglia → dystonia

- Some cases may evolve to "Status marmoratus"
  - Caused by selective neuronal necrosis and overgrowth of myelin of oligodendrocyte in the basal ganglia and thalamus
  - marble-like appearance



B. Parasagittal cerebral injury

- Characteristically, **full term infant**

- Parasagittal area
  - **borderline zone** between major arterial territories in term

  Cf) Rich anastomosis between meningeal arteries in preterm
  → preserve blood flow to cerebral cortex & subcortical WM

- Symptom
  - U/Ex > L/Ex, Proximal > Distal

C. Periventricular leukomalacia (PVL)

- PVL
  - Necrosis (softening) of white matter around the ventricles
  - common in **preterm** infants
  - Two basic components
    - Focal necrosis vs more diffuse
    - cystic PVL → the highest risk of developing CP

- Being born **preterm** dose not cause brain damage but is a **risk factor.**

C. Periventricular leukomalacia (PVL)

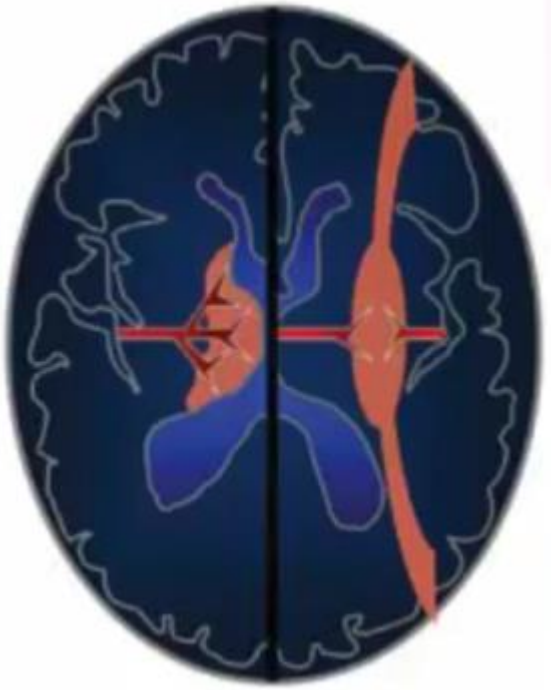
- **Brain vulnerability**

  between 26-34 wks of GA

- **Vascular anatomical and physiological factor**
  - vascular end zones and border zones in periventricular white matter
  - Low blood flow in white matter (5.0ml/100mg/min)

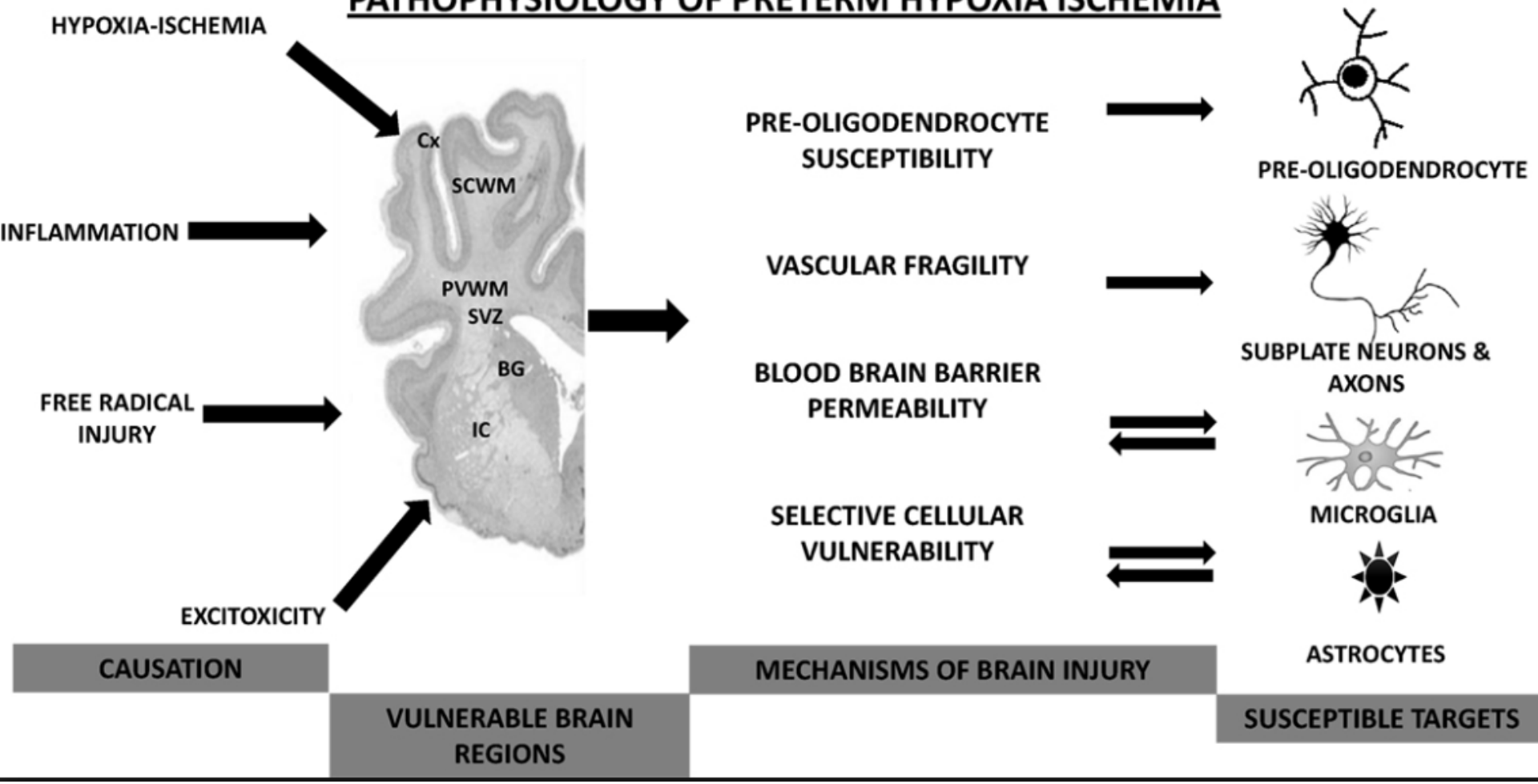
    cf) Adult: 50ml/100mg/min
  - Impaired cerebrovascular autoregulation
  - More vulnerable pre-oligodendrocyte to free radical injury

Pattern of brain injury in hypoperfusion



Border zone	
Preterm	Term infant
Periventricular white matter	Subcortical & parasagittal white matter

PATHOPHYSIOLOGY OF PRETERM HYPOXIA ISCHEMIA

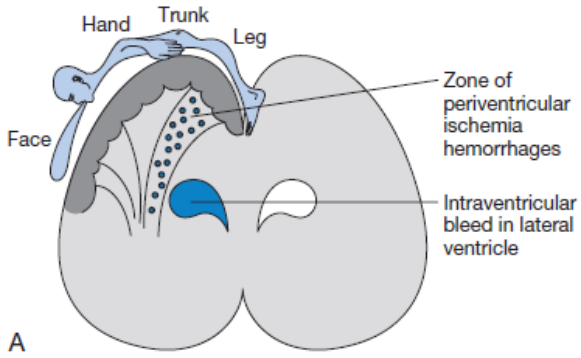


C. Periventricular leukomalacia (PVL)

- Causative pathologies of periventricular WM injury
  - Ischemia – hypoxia
  - Maternal chorioamnionitis
    - Premature rupture of the membrane with resulting ascending maternal infection
    - Maternal cytokines are believed to have an adverse effect on the oligodendroglia (the cells that are responsible for WM production)
  - Hypocarbia by overventilation

C. Periventricular leukomalacia (PVL)

- Symptom
  - ↑ **Spastic diplegia**
  - more affects the L/Ex

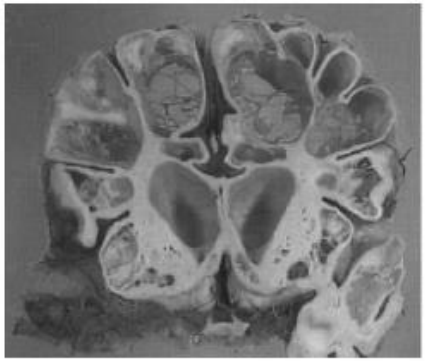


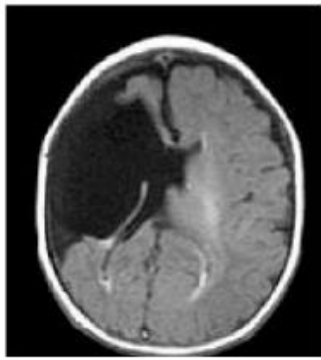
- Relationship of imaging of PVL & development of CP
  - Cystic PVL have the highest risk of developing CP
  - Premature infants with more severe bleeds have a worse prognosis for survival and a higher risk for developing CP
  - However, no specific parameters that fully predict risk of developing CP or the severity of CP in an individual child.

- Clinically, more term babies suffered from HIE than preterm babies. Pathologically, more premature babies suffered from HIE than term babies

D. Focal and multifocal ischemic brain necrosis

- Ischemic necrosis within the distribution of single (or multiple) major cerebral vessel
  - hydranencephaly
  - Porencephaly
  - multiple cystic encephalomalacia
- Hypercoagulability
  - Factor V Leiden mutation (resistance to activated protein C)
  - Antiphospholipid syndrome
- 2nd trimestear~1st postnatal weeks or months
  - high water content, immature myelination, deficient astrocytic response





림 16-4 공뇌증(porencephaly)의 육안적 소견(1)[0] 및 뇌자기공명촬영 소견(2; 생후 3개월 남아).

HIE

- Major public health issue
- In developed countries, moderate or severe HIE in 1 per 1000 live births

- Mortality between 10% and 60% of these infants with moderate or severe HIE die during the neonatal period.
- At least 25% of the survivors have significant major long-term neurodevelopmental sequelae including MR, CP, and epilepsy.
- Hypoxic ischemic encephalopathy is the primary cause of 15% to 28% of cerebral palsy among children.
- Presence of seizure increase chance of cerebral palsy by 50-70 times.

Sequelaes of HIE

- Neurodevelopmental impairment
- Neuromotor impairments (CP)
- Mental retardation
- Epilepsia
- Behavioral and cognitive deficits
- Blindness and hearing loss
- Intellectual limitation,
- Language problems,

Shankaran S. Childhood outcomes after hypothermia for neonatal encephalopathy. NEJM. 2012

- **Term infant**
- Parasagittal injury, selective neuronal necrosis,

  focal/multifocal ischemia, status marmoratus
- Proximal spastic quadriparesis, spastic CP, spastic hemiparesis, cognitive defects, seizure, extra pyramidal CP

- **Preterm infant**
- Periventricular leukomalacia, IVH
- Spastic diplegia, visual impairment

2. Germinal matrix – Interventricular hemorrhage (GMH-IVH)

- **Germinal matrix**
  - located above the caudate nucleus, in the floor of the lateral ventricle, and caudothalamic groove
  - Proliferation and migration of glial and neuronal precursors
  - By 35-36 weeks gestation the germinal matrix has essentially disappeared

- Fragility of Germinal matrix
  - highly cellular and rich blood supply region
  - irregular endothelial-lined vessels→ extremely sensitive to hypoxia and changes in perfusion pressure

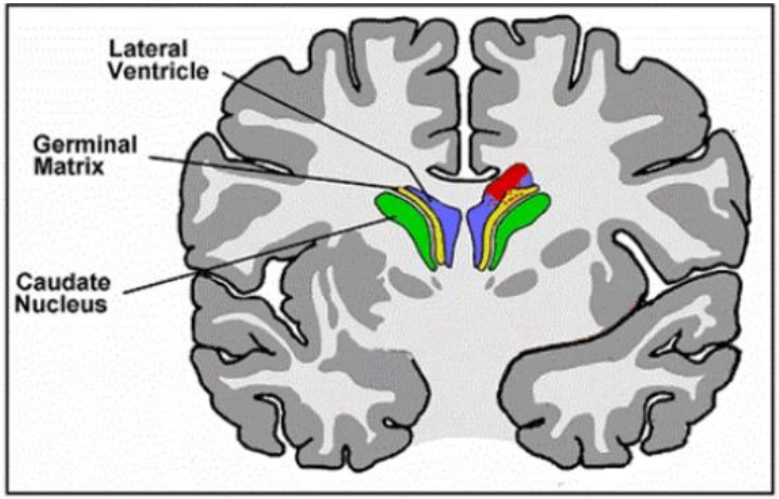
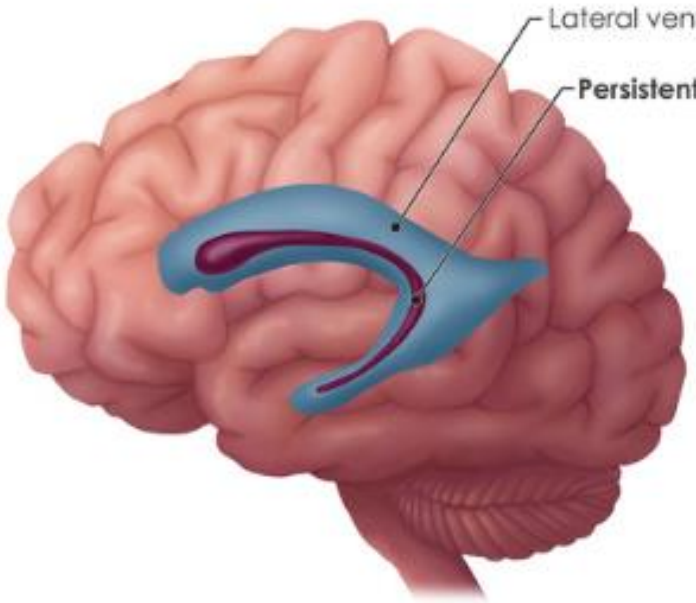


Figure 1: Location of a germinal matrix between each lateral ventricle and caudate nucleus, with bleeding into the ventricle on the right.

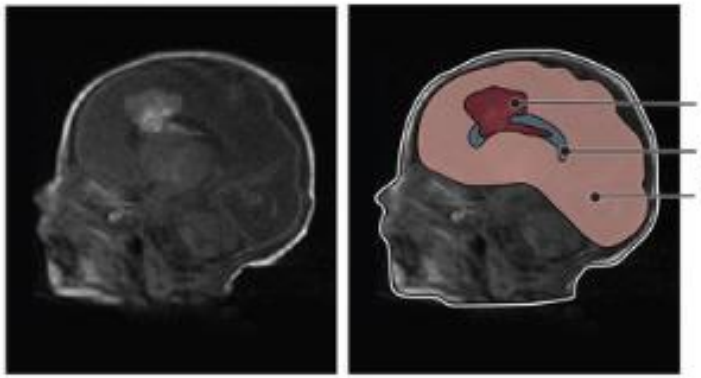
Torrison et. al. v. Colwill et. al.

Plaintiff's Anatomy



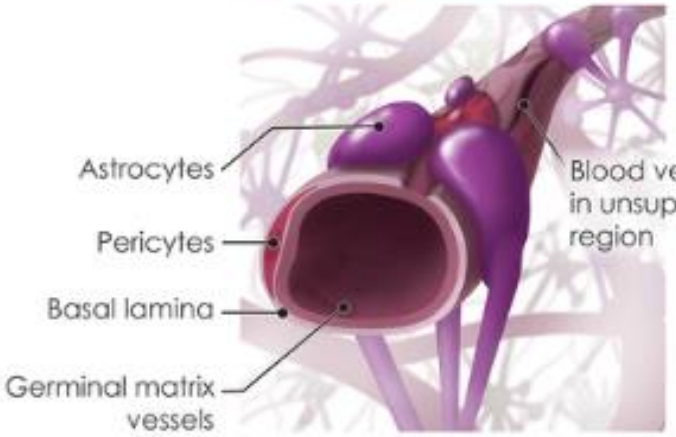
Plaintiff's brain at birth

Germinal Matrix Hemorrhage



Hemorrhage begins with "bleeding restricted to this region [germinal matrix]". This is followed by "ventricular enlargement" and can result in "white matter damage"

Features of the Germinal Matrix



Characteristics making the germinal matrix more prone to hemorrhage

- Large vessel size
- Lack of sufficient support (by astrocytes, pericytes, and basal lamina)
- High density of blood vessels

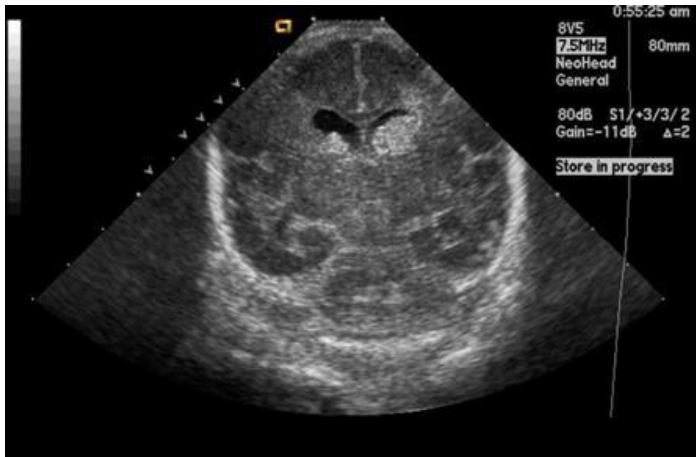
2. GMH-IVH

↑ Blood pressure
↑ blood flow

→ Rupture & hemorrhage into germinal matrix

→ Venous infarction & hydrocephalus

- GMH– IVH
  - bleeding into the subependymal germinal matrix
    ± subsequent rupture into the lateral ventricle
  - frequent lesion in **premature babies**



2. GMH-IVH

- Severity
  - Grade I : germinal hemorrhage only
  - Grade II : IVH without ventricular dilatation
  - Grade III : ventricular system enlargement
  - Grade IV : periventricular hemorrhage and infarction

- Prognostic significance
  - No GMH-IVH have a better survival prognosis
  - Risk of CP : 9%, 11%, 36%, 76% (Grade I,II,III,IV)

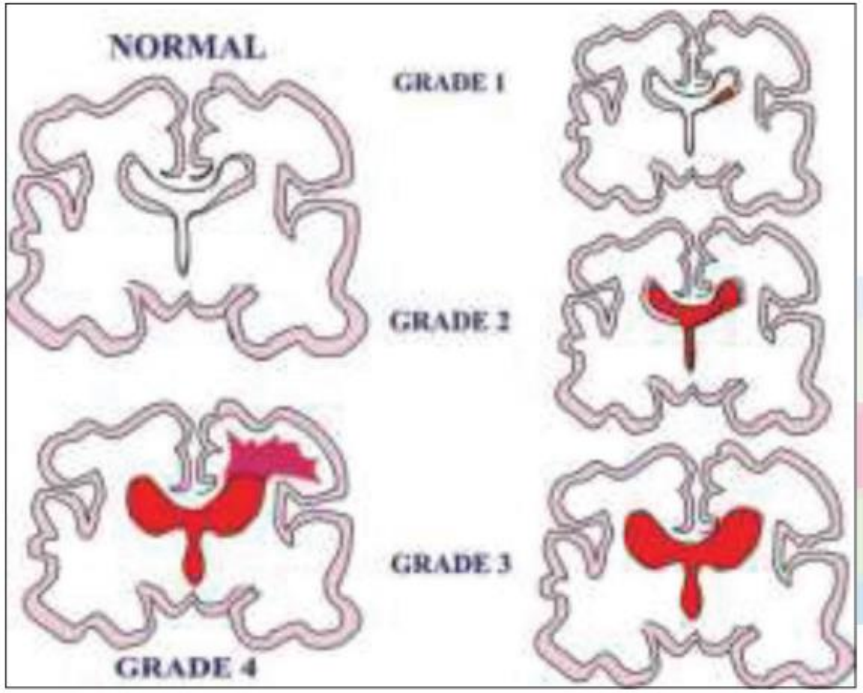
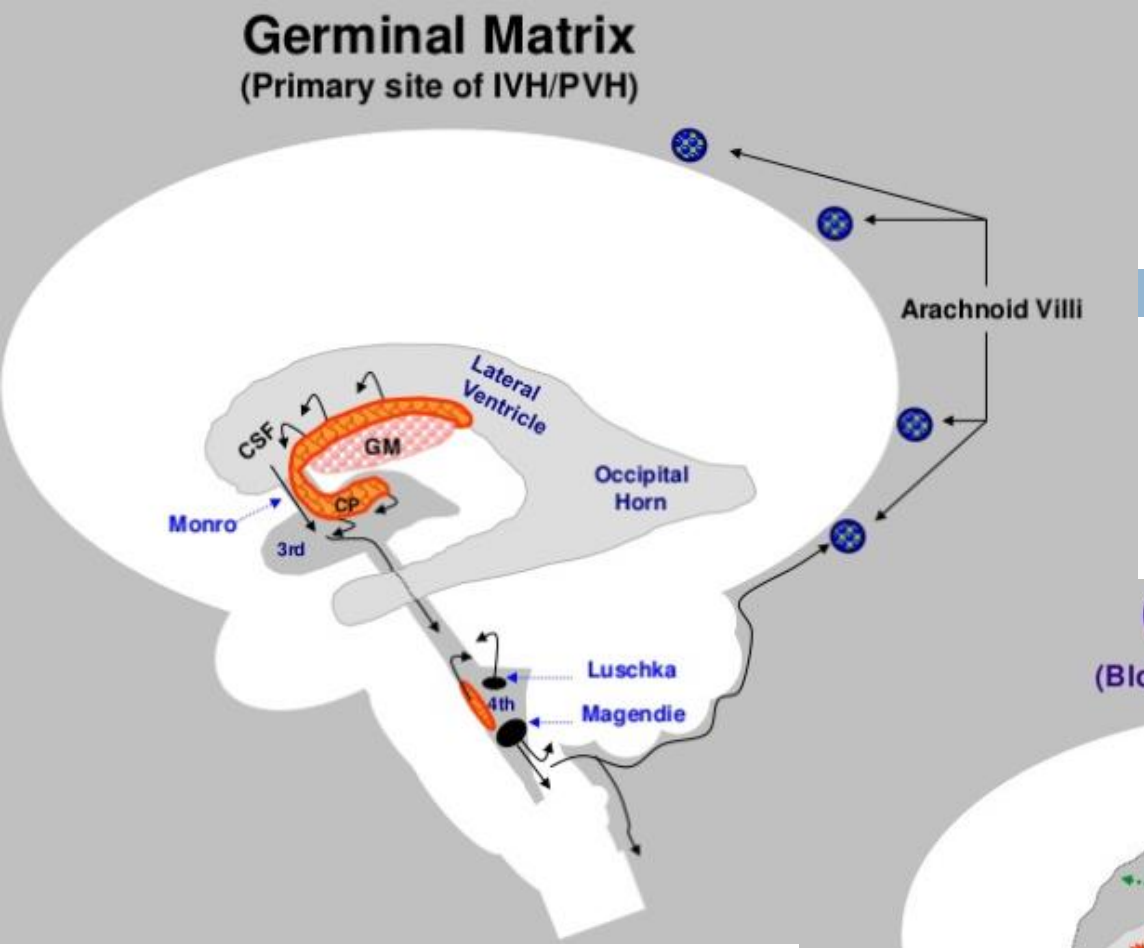
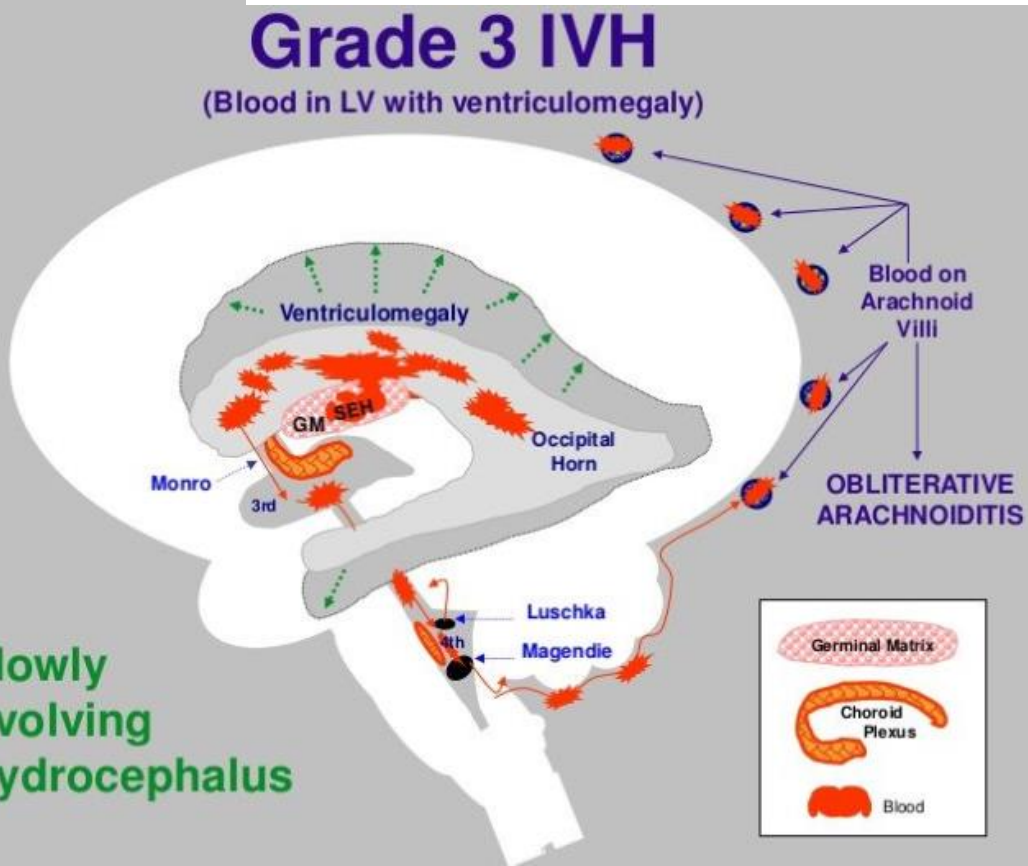
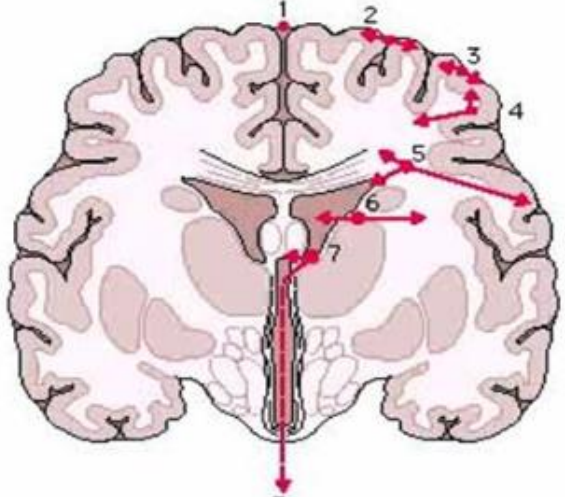


Figure 12B: Diagrammatic representation of IVH classification by Papile (modified)


Germinal Matrix
(Primary site of IVH/PVH)
Arachnoid Villi
Lateral Ventricle
CSF
GM
CP
Monro
3rd
Occipital Horn
Luschka
4th
Magendie


Grade 3 IVH
(Blood in LV with ventriculomegaly)
Blood on Arachnoid Villi
Ventriculomegaly
GM
SEH
Occipital Horn
Monro
3rd
OBLITERATIVE ARACHNOIDITIS
Luschka
4th
Magendie
Slowly Evolving Hydrocephalus
Germinal Matrix
Choroid Plexus
Blood



Key

1 Subdural hemorrhage
2 Subarachnoid hemorrhage
3 Subpial hemorrhage
4 Intra cerebral hemorrhage or hemorrhagic infarction
5 White matter hemorrhage or hemorrhagic infarction
6 Subependymal germinal plate/matrix hemorrhage
7 Choroid plexus hemorrhage

INTRACRANIAL HEMORRHAGE

Term Infant

- Commonest are subdural, subarachnoid or subtentorial.
- Mostly related to Birth trauma, HIE, coagulopathies and undetermined causes.

Preterm Infant

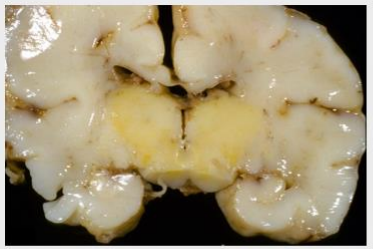
- Commonest is bleeding from the subependymal germinal matrix and may result in intraventricular or periventricular hemorrhage.
- White matter injury due to hypoxic ischaemia and infections.

Perinatal arterial Ischaemic stroke, sinovenous thrombosis and perinatal hemorrhagic stroke, Trauma are responsible for hemorrhages in TERM / PRETERM infants.

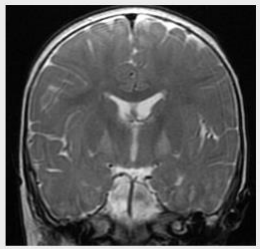
3. Bilirubin encephalopathy (Kernicterus)

- Bilirubin
  - Production by breakdown of fetal RBC
  - **Unbound**, **unconjugated**, circulating bilirubin crosses the blood-brain barrier and, because it is lipid soluble, it penetrates neuronal and glial membranes
- kernicterus
  - Immaturity of the blood-brain barrier probably plays
  - Metabolic acidosis by perinatal asphyxia

    : high unconjugated bilirubin with relatively modest levels of bilirubin → kernicterus
  - **special affinity** for the basal ganglia and nucleus of oculomotor and cochlear nerves.



Kernicterus



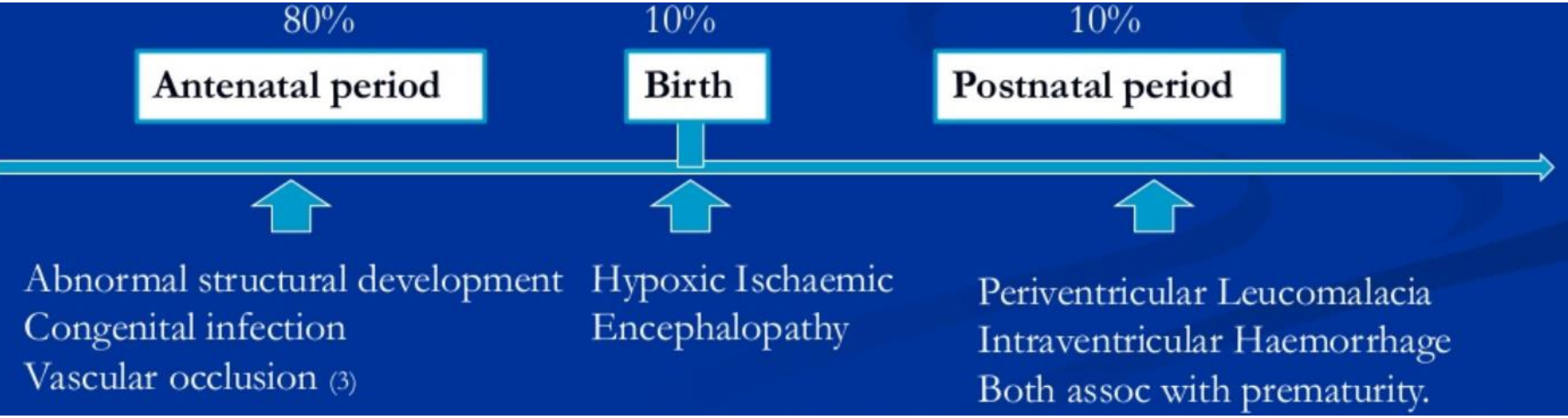
High T2 signal in globus pallidus

3. Bilirubin encephalopathy (Kernicterus)

- Symptoms
  - Extrapyramidal syndrome, **athetoid**
  - **gaze abnormality**
  - **hearing loss** (esp. sensorineural)
  - Mental retardation, relatively well maintained at 50%
  - Often also epilepsy

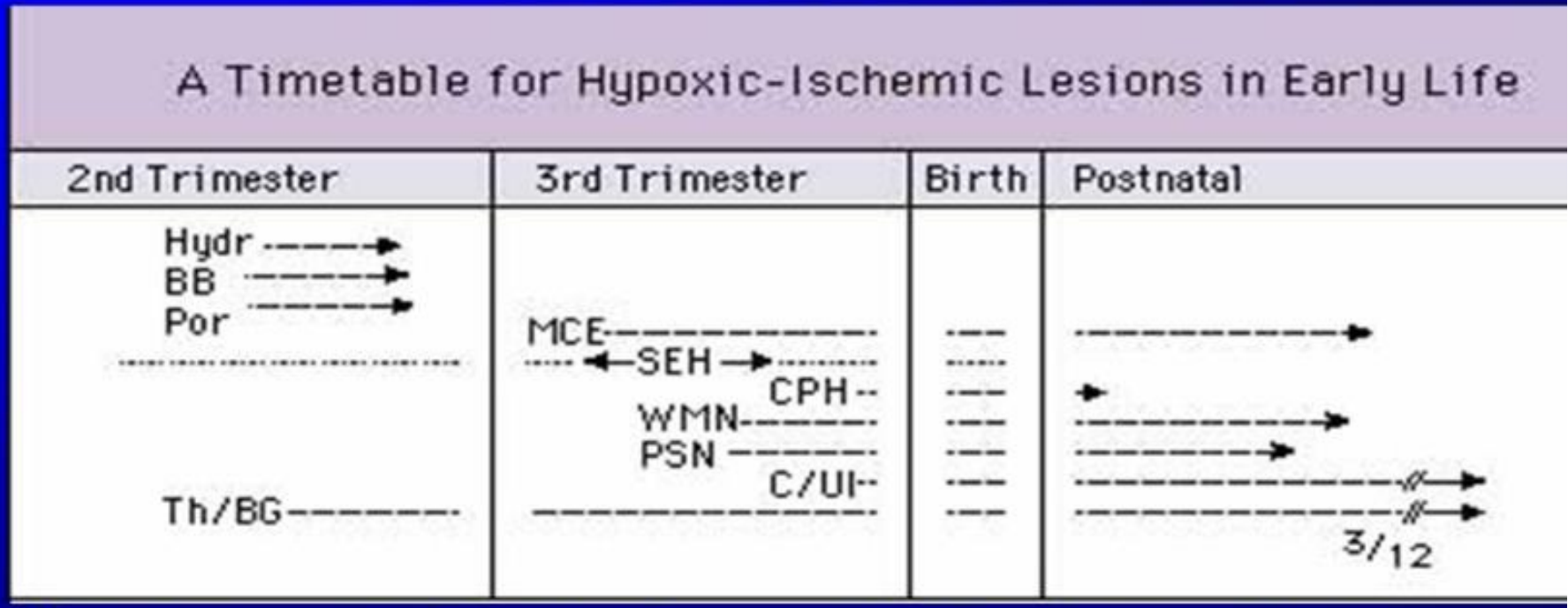
- Causes
  - hemolytic disease
    - Rh incompatibility, hereditary spherocytosis
  - inability of the liver to conjugate bilirubin

Timing of perinatal brain injury



Hypoxia\Ischemia: General concepts

- Timing of lesion during development critical to determining type of lesion produced



(Hydr = hydranencephaly, BB=basket brain, Por=porencephaly, MCE=multicystic encephalopathy SHE=germinal matrix hemorrhage, CPH=choroid plexus hemorrhage, WMN=white matter necrosis PSN=pontosubicular necrosis, C/Ul=cortical necrosis/ulegyria, Th/BG=thalamic/basal ganglia lesions)

Modified from *Neuropathology*, Ellison and Love, 1998

Pre-conceptual events

- Genetic vulnerability
  - Factor V Leiden
  - MTHFR (methylenetetrahydrofolate reductase)
  - Lymphotoxin α
  - Tumor necrosis factor-α
  - eNOS, mannose binding lectin

- Maternal factor
  - age : <20yr, >40yr
  - Smoking, alcohol, History of stillbirth, low socioeconomic status
  - Intellectual disability, seizure, thyroid disease

Early antenatal factors

- Chromosomal abnormalities
  - Association with early cell division after fertilization
  - Cause overall developmental delay rather than CP

- Early cerebral malformation
  - Anencephaly : most severe
  - Disorders of neuronal proliferation
    - hemimegalencephaly
  - Disorders of neuronal migration
    - Lissencephaly, heterotopia
  - Disorders of neuronal organization
    - polymicrogyria, schizencephaly

Antenatal factors

- Congenital infection
  - Rubella : Significant reduction in immunization
    - Very commonly will have mental retardation, however, only 15% develop CP
  - CMV : m/c infectious cause of CP
    - 90% of children with mental retardation and deafness, 50% develop CP or motor defects
  - Toxoplasmosis : house cat (most common host)
    - *Toxoplasma gondii*, intracelluar parasite
    - 30% of children are left with CP and mental retardation
  - Neonatal herpes simplex infection : high mortality rate
    - 30-60% of survivors have some neurologic sequelae, CP is not common
  - In utero varicella zoster infection : High rate of CP

Antenatal factors

- Chorioamnionitis
  - ↑ risk of CP and PVL in preterm and term infants
- Preeclampsia
  - ↑ risk of CP in term
  - Not increase in preterm

    : ↑ cathecholamine → fetal maturation
- Twin : ↑ IUGR, malformation
- iodine deficiency
- Alcohol

Intrapartum factors

- Placental abruption, cord prolapse, rupture of uterus
  - CP risk ↑, but rare
- Premature rupture of membranes
- Abnormal duration of labor
- Fetal presentation…

→ Perinatal asphyxia associated CP: 6-8%

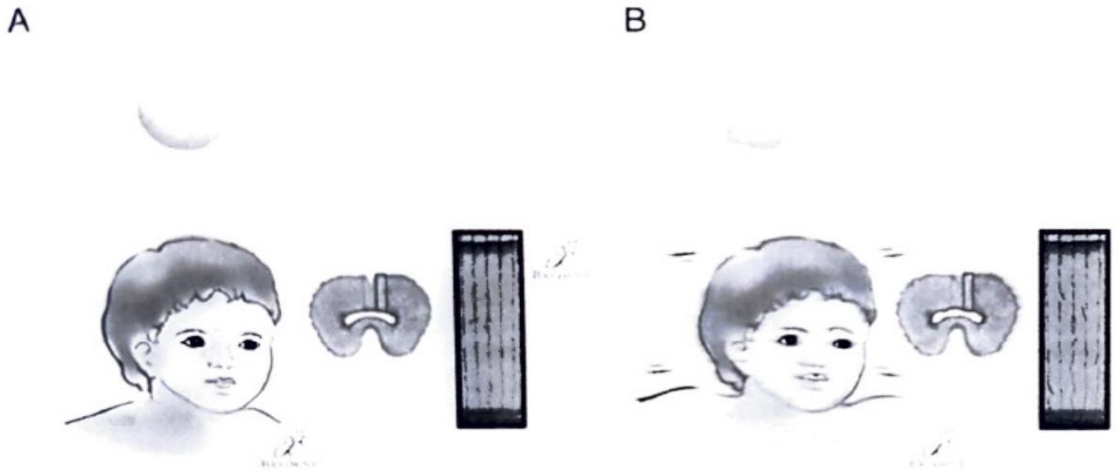
Postnatal factors

- Postnatal brain impairment
  - Many clinicians regard the age of 2 years
  - Vitamin K IM injection at birth : bleeding risk ↓

- Major cause
  - Bacterial infection, particularly meningitis
    - 30-50% of survivors having CP
    - Hemophilus influenza type B: significant reduction in immunization
  - Blunt head trauma
    - Child abuse, falls, or motor vehicle accidents
  - Febrile seizure
    - cause in developing country

Postnatal factors

- Shaken baby syndrome
  - Vigorous shaking cause stretching, shearing, and tearing of long axons and capillaries in the cortex of the brain
  - Often have a severe spastic quadriplegia with poor prognosis for improvement
  - Concomitant profound mental retardation



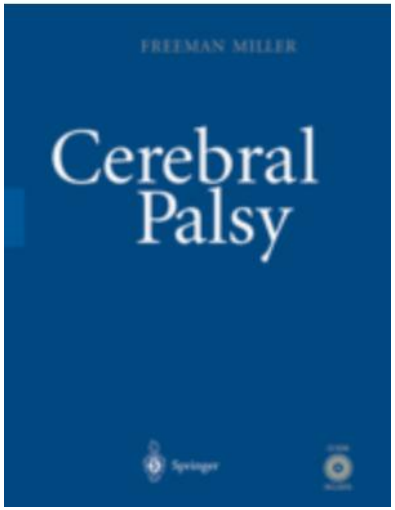
Perinatal brain injury

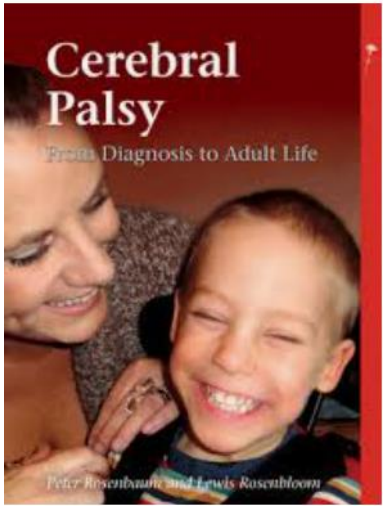
Table 1
Aspects of common etiologies of perinatal brain injury

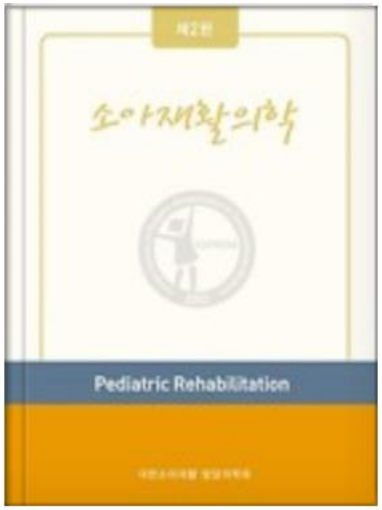
Perinatal Brain Injury Type	Gestational Age	Mechanism of Injury	Neuropathologic Findings	Preventive Measures	References
Hypoxic–ischemic encephalopathy	Late preterm, term (>35 wk)	Hypoxia–ischemia leading to common pathway of injury	Diffuse gray and white matter injury affecting most vulnerable regions of brain	Therapeutic hypothermia Postnatal erythropoietin	5–8
Intraventricular hemorrhage	Preterm (primarily <32 wk)	Injury to fragile premature vessels of germinal matrix	Germinal matrix bleeding with extension into ventricular system	Antenatal corticosteroids Delayed umbilical cord clamping	9–11
Periventricular leukomalacia	Preterm (primarily <32 wk)	Hypoperfusion to border zone regions of brain	Periventricular focal necrosis, cystic formation, or diffuse white matter injury	None	18
Perinatal stroke	Preterm, term	Regional ischemia owing to arterial or sinovenous occlusion or hemorrhagic infarction	Regional infarction owing to vascular occlusion or hemorrhage	None	12–14
Cerebral palsy	Preterm, term	Multifactorial, only 10%–20% of cases owing to an intrapartum hypoxic–ischemic event	Clinical syndrome with variable findings depending on underlying etiology	Magnesium sulfate	6,15–17

Novak CM, Ozen, M, Burd I: Perinatal Brain Injury: Mechanisms, Prevention, and Outcomes, Clin Perinatol 45 (2018) 357–375

Reference







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아기는 자라면서 튼튼해지고
지혜가 충만해졌으며, 하느님의 총애를 받았다.
루카 2,40