THE CHRONOLOGY OF FETAL AND NEONATAL HIE

• Disruptions
• Haemorrhages
• White matter lesions
• Grey matter lesions
• Chronic lesions
• Pathogenic/developmental considerations
Theme: timing is crucial
Timetable for hypoxic-ischemic lesions

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<th>2nd trimester</th>
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Hydr = hydraencephaly, BB = basket brain, Por = porencephaly, MCE = multicystic encephalopathy, SEH = subependymal hemorrhage, CPH = choroid plexus hemorrhage, WMN = white matter necrosis, PSN = pontosubicular necrosis, C/UI = cortical necrosis/ulegria, Th/BG = thalamus/basal ganglia damage

*Multiple lesions with the same cause*
HIE: intrauterine disruptions

- Smooth walled defects of midgestation
  - Porencephaly
  - Schizencephaly
  - Hydranencephaly

Irregular destruction and repair of late gestation
- Multicystic encephalopathy
Hydranencephaly

- Attempted abortion
- Maternal poisoning
- Attempted suicide
- Severe hypoxia
- Anaphylactic shock
- Twinning
- Fetal infection
- 18-27wk gestation
- Symmetry/ topography
- Animal experiments
Schizencephaly

32 (19) wg

4y
Multicystic encephalopathy

36wg
1\textsuperscript{st} twin
Multicystic encephalopathy

Conjoined twin

Birth asphyxia
Hemorrhages

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

Petechiae

Local haematoma

Basal cistern
Subpial haemorrhage
Germinal matrix- subependymal haemorrhage

Grade 1
Germinal matrix- subependymal hemorrhage

Grade 2

Grade 3
Germinal matrix- subependymal hemorrhage

Grade 4

Mixed hemorrhage & infarct

Hemorrhagic infarct

Terminal vein thrombosis
SEH- Pathogenesis

- low birth wt premature infants <34wg
- persistent large highly cellular matrix zone
- anastomosing capillaries without supporting stroma
- border zone of striate and thalamic arteries
- draining into thin walled venules progressive dilatation >23w, but only thicken >34w
- Hypoxic stress leading to loss of autoregulation, over-perfusion, and disruption of these fragile vessels
- Poor hemostasis with excess fibrinolytic activity within the matrix
- Morphologic evidence for ruptured venules showing endothelial necrosis
Choroid plexus hemorrhage
Cerebellar haemorrhage
White matter lesions

Periventricular leukomalacia (PVL)
Telencephalic leucoencephalopathy (TLE)
Clinical Significance of Perinatal White Matter Injury (PWMI)

- 60,000 infants born each year (in the US) with bw < 1500 gm; 50% have evidence of cerebral white matter injury on MRI
- PVL/PWMI is a strong predictor of mental retardation and cerebral palsy
- Greater than 60% of infants with PVL later develop cerebral palsy
- The incidence of non-cystic PVL/PWMI and cerebral palsy has not decreased over time
PVL - massive necrosis

Telencephalic leukoencephalopathy
Chronic lesions: white matter
White matter injury-pathogenesis

- Blood flow
- Excitotoxity
- Oxidative stress
- Cytokines
Figure 1. The macroscopic appearance of cystic PVL

Haynes et al, 2005
**Excitotoxicity**

- Altered glutamate homeostasis
- Promotes Ca^{2+} influx

**Free Radical Attack**

- Developmental delay of antioxidant enzymes
- Accumulation of H_{2}O_{2} leads to Fe^{2+}-mediated conversion to OH\(^{-}\) by Fenton rxn
- Nitrative stress may be triggered by reactive astrocytes
- Microglia secrete ROS/RNS and cytokines
Immature AMPA receptors flux Ca++ like NMDA receptors until mGluR2 metabotropic receptor expressed.

NMDA first receptors to be expressed, Ca++ permeable.

mGluR2 are not expressed until postnatal period, once expressed AMPA receptors become Ca++ impermeable.

Johnson MV, 2005
Why these receptors?

Oligodendrocytes: KA/AMPA
  Possible role: link between activity and myelination
  Timing: 23-32 weeks gestation

Neurons: Ca$^{++}$ permeable AMPA receptors
  More effective in activity-dependent synaptic plasticity
Grey matter lesions: patterns of cortical involvement

- Ribbon effect
- Haemorrhagic infarct
- Middle cerebral infarct
- Boundary zone
- Laminar necrosis
Grey matter lesions: subcortical patterns

Pontosubicular necrosis

Internal cerebellar folial atrophy

Thalamus, ferrugination

Reticular core necrosis
Moebius syndrome

Congenital facial diplegia with bilateral abducens palsy
Neonate presenting with an expressionless face and internal strabismus
Moebius syndrome

27wg, to G5
3 therapeutic
and 1 spontaneous abortion
Chronic lesions: grey matter

ulegyria

marbling

Basal ganglia cyst
Unilateral Hypertrophy of the Pyramidal Tract
Kernicterus
Kernicterus

- Accumulation of bilirubin resulting from XS production or insufficient conjugation & excretion.
- Unconjugated bn is toxic
- Bilirubin 30mg/dl in Hemolytic disease of newborn, virtually unknown
- Small preterms: asphyxia acidosis hypoglycemia or septicemia, levels >10mg/dl. Damaged blood-brain barrier and reduced albumen binding capacity (liver disease, drug Rx)