Disruption of Fetal Brain Development

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Brain Malformations

Primary genetic causes

Primary environmental causes
Brain Malformations

Primary genetic causes

Epigenetic changes

IEM

Primary environmental causes
Dysgenetic or disruption? Why clinicians care

Critical for informed counseling

• Prognostication for this pregnancy
  • Genetic influences may have more pervasive developmental effects missed by clinical imaging
  • Genetic mechanisms are largely intractable
  • Environmental insults may be interrupted
• Recurrence risk in future pregnancies
Critical and vulnerable periods in brain development

A critical period is

- a phase during normal brain development when environmental (internal or external) factors may cause major and irreversible disruption in brain development
- characterized by normally rapid and/or major changes in specific developmental event, e.g., the surge in late gestation cortical organization and growth

A vulnerable period is

- a phase during normal brain development when the neural structure/system is particularly susceptible to noxious insult or deprivation of normal influences
Normal fetal brain development

- Overlapping critical periods
- Progressive events
- Regressive events (developmental apoptosis, selective elimination of cellular processes)
- Noxious influences may affect both types of developmental event and reduce brain’s compensatory response to injury
Brain malformations in the fetus

Diagnostic challenges

- Genetic and environmental factors may disrupt normal brain development in similar ways.
- Cicatricial changes may be subtle or absent if insult occurs before 20-24 weeks.
- Hemorrhage may be difficult to see on fetal MRI and heme changes may have vanished by birth.
Etiologies of Fetal Brain Disruption

Hypoxic-ischemic/reperfusion
  • Global HI/R insults
  • Focal HI/R insults

Hemorrhage

Infection

Toxins
  • Exogenous
  • Endogenous

Other
Fetal vaso-occlusive stroke with regional disruption of development
Severe prematurity, cystic PVL, and polymicrogyria
Developmental effects of fetal viral encephalitis

Early gestation onset CMV encephalitis

Early gestation onset CMV encephalitis
Inborn errors of metabolism
Brain malformations
Cocaine is a monoamine (DA, NE, 5HT) reuptake inhibitor which disrupts brain development by

- Disturbing neuronal formation, proliferation, migration, and early connectivity
- Vasoconstriction in fetal brain, placenta, and umbilical vein
- Intrauterine stress and altered fetal programming
The road ahead….
Beyond pattern recognition

- Large populations of infants with noxious fetal exposures and obvious neurodevelopmental sequelae but no obvious ‘lesions’ by current conventional MRI

- Advances in quantitative MRI/MRS will play a critical role in identifying the anatomic substrate
Summary and conclusions