PERINATAL NEUROPATHOLOGY: A PRACTICAL APPROACH

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Disclosures

-Cornelli Consulting, Milan, Italy: Hold a joint patent for a glycosaminoglycan for the treatment of Alzheimer’s disease and other related neurological disorders, ie. anti-anxiety effects

-Editor-in-Chief, Journal of Neuropathology and Experimental Neurology, American Association of Neuropathologists

-Member of the Medical and Science Advisory Board for Ceremark Pharma LLC
GROSS DESCRIPTION:
Autopsy Brain Cutting

Perinatal Brain Cutting

Gross description
The brain is carefully removed and fixed in formalin (with or without acetic acid) for a minimum of 7-10 days prior to full gross examination. After fixation, the brain is [intact and shows two cerebral hemispheres / mostly intact / partially fragmented / completely fragmented]. The external surface of the brain is [white and shiny / dusky] and there [is / is not] anterior-posterior blunting. The leptomeninges [appear congested and/or show possible subarachnoid hemorrhage].

[No/primary/secondary/tertiary] sulcation is present. The calcarine fissure [is / is not] present. The parieto-occipital fissure [is / is not] present. [Add any other details about sulcation pattern______________________________]. The corpus callosum [is/is not] present.

The [right / left] hemisphere is serially sectioned and shows [describe any lesions or findings such as, intra/periventricular hemorrhage, parenchymal hemorrhage(s), white matter cystic change etc.]

__________________________________________

[Other notes]

Sections:
B1 - brainstem and cerebellum
B2 - frontal lobe
B3 - temporal lobe with hippocampus
B4 - parietal lobe
B5 - occipital lobe
B6 - thalamus/subcortical nuclei
B7 -
B8 -
Neuronal Maturation

Pseudoverrucous Lamination (Normal up to 28 weeks)
Acute Perinatal Stress

Subarachnoid Hemorrhages
Germinal Matrix Hemorrhages
Choroid Plexus Hemorrhages
Hypoxic-Ischemic Changes
Acute Perinatal Stress

Subarachnoid Hemorrhages

**Germinal Matrix Hemorrhages**

Choroid Plexus Hemorrhages

Hypoxic-Ischemic Changes

**GERMINAL MATRIX HEMORRHAGE**
Acute Perinatal Stress

Subarachnoid Hemorrhages
Germinal Matrix Hemorrhages
Choroid Plexus Hemorrhages
**Hypoxic-Ischemic Changes**
Metabolic Encephalopathy
Alzheimer Type II Astrocytes (Metabolic Encephalopathy)
Shrunken Eosinophilic Neurons (Acute Anoxic-Ischemic Encephalopathy)

Kinney and Volpe (Volpe’s Neuropathology of Newborn 6th Ed)

Pons
Shrunken Eosinophilic Neurons (Acute Anoxic-Ischemic Encephalopathy)
Pons
Shrunken Eosinophilic Neurons
(Acute Anoxic-Ischemic Encephalopathy)

Thalamus
Shrunken Eosinophilic Neurons
(Acute Anoxic-Ischemic Encephalopathy)
Prolonged Perinatal Stress

Chronic Hypoxic-Ischemic Changes
  Periventricular Leukomalacia
  Parenchymal Calcifications

Prolonged Perinatal Stress

Chronic Hypoxic-Ischemic Changes
  Pontosubicular Necrosis
  Periventricular Leukomalacia
  Parenchymal Calcifications
Nuclear Karyorrhexis

From Semanticscholar.org
Prolonged Perinatal Stress

Chronic Hypoxic-Ischemic Changes

**Periventricular Leukomalacia**

Parenchymal Calcifications

Oushsc.edu  Periventricular Leukomalacia
Major Congenital Malformations

Agenesis of the Corpus Callosum
  Down Syndrome
  Holoprosencephaly
  Anencephaly
Lissencephaly Spectrum
  Polymicrogyria
  Heterotopias

Agenesis of the Corpus Callosum
Agenesis of the Corpus Callosum

Agenesis of the Corpus Callosum with Hydrocephalus
Agenesis of the Corpus Callosum

• Complete and incomplete (partial) types
  – Partial is usually only missing the splenium
• Isolated (silent clinically or subtle) or seen in association with other malformations (i.e. holoprosencephaly)
• May be sporadic but typically associated with syndromes: Aicardi, Andermann, Meckel
• Possible pathogenesis:
  – Probst bundle of misdirected fibers
  – Mechanical defect suggested by hamartoma/ lipoma

A. Viaene Pediatric Neuropathology: Malformations AANP Teaching Rounds, Feb 24, 2021

Holoprosencephaly
Holoprosencephaly

Pediatric Neuropathology: A Text-Atlas Figures 2.7-3 and 2.7-5

Holoprosencephaly

Berry, RS and Andrews SW, Images in Forensic Pathology Acad Forensic Pathol (2014) 4: 258-260
Holoprosencephaly Etiology

- Material diabetes mellitus
- Infections: Toxoplasmosis, syphilis, rubella
- Teratogens: Ethanol, retinoic acid, cholesterol synthesis inhibitors
- Genetic factors:
  - Cytogenetic abnormalities seen in 50% of cases
  - **Trisomy 13 most frequent**
    - Smith-Lemli-Opitz syndrome (DHCR7)
    - Other Mutations

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Anencephaly
Anencephaly

• In the United States the prevalence of anencephaly was 9.4 per 100,000 live births in 2001

• Between 1999 and 2004, there were 2,116 cases reported
  – though this number greatly underestimates the actual occurrence because many anencephalic fetuses are spontaneously aborted or electively terminated

Anencephaly

• Anencephaly is a severe defect which is ultimately incompatible with life
  – Infants born alive generally die within hours with some surviving a few days or rarely a few weeks
Anencephaly

- Anencephaly is characterized by an open defect in the calvaria (skullcap) and the skin, causing the cranial neural tissue to be exposed.
- Neural tissue that is exposed to amniotic fluid in utero is damaged.
  - Results in a fibrotic, vascular mass with scant neural tissue, termed area cerebrovasculosa.

Anencephaly

- Portions of the skull including the frontal, parietal and occipital bones are absent giving the characteristic appearance of “bulging” eyes (note eye are formed).
- Underdevelopment of the pituitary gland (posterior usually not anterior) with adrenal gland hypoplasia.
- Absent neck.
Anencephaly

- Cranial and facial abnormalities are also seen in anencephaly
  - Result of abnormal induction of neural crest tissue
- The forebrain and variable amounts of the upper brainstem are typically involved

Head 11.1 cm in circumference (50th percentile = 17.3 cm)
Approximate biparietal diameter 2.9 cm (50th percentile = 4.71 cm)
Inner canthal distance 1.0 cm (50th percentile = 1.25 cm)
Absent skull bones and spinal rachischisis, with a portion of red soft tissue located in the left parietal area ("area cerebrovasulosa").
LEPTOMENINGES WITH "AREA CEREBROVASULOSA"
Embryology

- Closure of the cranial neuropore occurs around 3-4 weeks after conception.
- Lack of closure results in the absence of the calvarium and the brain.
- Neural tissue that is exposed to the in utero environment is damaged resulting in a fibrotic, vascular mass with scant neural tissue remaining.
  - This is known as “area cerebrovasculosa”

Associated Abnormalities

- Other common abnormalities seen with anencephaly are cardiac, pulmonary, renal and skeletal.
- Affected by anencephaly and rachischisis:
  - Renal defects are seen in 17%.
  - Cardiac defects are seen in 4%.
Lissencephaly/Agyria

- Smooth or unconvoluted: agyria or lissencephaly
- Reduced number and widened sulci: Pachygyria or macrogyria
- Histology:
  - Agyria with or without 4 cortical layers = Lissencephaly type I (Miller-Dieker)
  - Lissencephaly Type II (Cerebro-ocular dysplasia)

Appearance

- Small, misshapen skull, low brain weight
  - Abnormal face
- Thickened cortical ribbon with reduced white matter
- Ventricular dilation and nodular heterotopias
- Miller-Dieker best known syndrome
Agyria in Lissencephaly Type I Miller-Dieker
The cortical surface is smooth and the ribbon greatly thickened, while the greatly reduced white matter contains a large heterotopia (yellow arrow).
Lissencephaly Type II (Cerebro-ocular dysplasia) in an 18-week-old fetus

Age matched control
Polymicrogyria

- Hyperconvoluted cortical ribbon by miniature, thin gyri
- Varying degrees of neurologic disability
- Heterogonous Etiology:
  - Intrauterine ischemia
  - Intrauterine infection
  - X-linked Aicardi syndrome
  - Metabolic diseases
    - Pelizaeus-Merzbacher, Leigh’s syndrome, etc.
  - Peroxisomal disorders
    - Zellweger’s, ALD
Polymicrogyria
Polymicrogyria

• Peroxisomal, mitochondrial or chromosomal disorders
• Often associated with epilepsy, particularly myoclonic seizures
• Fetal insults: maternal hyperthermia, mercury poisoning, radiation
• Can be nodular or laminar (rarer)
Subependymal Heterotopias

Neurons in white matter
Major Perinatal Brain Infections

Bacterial Meningitis
Viral Meningitis
TORCH (Toxo, CMV and Herpes)

Routes of Entry

• Hematogenous
  – Most common
    • Usually arterial
    • Can be retrograde through anastomotic venous circulation of the face

• Direct implantation
  – Usually trauma
    • Can be iatrogenic – lumbar puncture

• Local extension
  – Sinus, oral, spinal osteomyelitis

• Via peripheral nervous system
  – Viral

• Indirect damage to the brain
  – Microbial toxins
  – Secondary Inflammatory responses
  – Immune-mediated (auto-immune antibodies)
Meningitis
Inflammation of the Meninges

• Usually bacterial (Acute)
• Viral (Self-limiting)
• Fungal (Immune-compromised)

Common Bacterial Causes

• Neonatal:
  – E. coli, group B strep.

• 3 months – 3 years:
  – Pneumococcus (Streptococcus pneumonia)
  – H. influenza – less common presently due to vaccination

• Young adults:
  – Neisseria meningitis

• Adults:
  – Pneumococcus

• Age extremes:
  – L. monocytogenes, Pneumococcus
Morphology

- Meninges are opaque and thickened
- Exudate
- Inflammation can extend into vessels causing vasculitis, thrombosis, and hemorrhage
- Leptomeningeal fibrosis with subsequent hydrocephalus may be long term sequelae, particularly due to the polysaccharides of *Pneumococcus*
CSF Findings

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<tr>
<th>ORGANISM</th>
<th>FLUID QUALITY</th>
<th>CELLS PRESENT</th>
<th>PROTEIN</th>
<th>GLUCOSE Relative to plasma levels</th>
<th>PRESSURE</th>
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<tbody>
<tr>
<td>BACTERIA</td>
<td>CLOUDY</td>
<td>PMNs</td>
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Viral Meningitis

- Usually self-limiting without complications
- Many possible agents
  - Mumps
  - Enteroviruses
  - EBV
  - Coxsackie
Meningeal and scanty perivascular infiltrate of lymphocytes

Encephalitis

General Features of Viral Encephalitis
Using Poliomyelitis as a Case Study

• Lytic infection of motor neurons (neurotropism) with encephalomyelitis
• Macroscopic lesions rare
Polio: Microscopic

- Usually worse than clinically apparent
- Anterior horn, motor nuclei of pons and medulla, reticular formation and cerebellar nuclei (*neurotropism*)
- *Lymphocytic cuffing*
- *Leptomeningeal inflammation*
- *Neuronophagia*

Meningeal and scanty perivascular infiltrate of lymphocytes
Microglial nodules (viral encephalitis)

© Elsevier 2005  Herpes Simplex
Herpes Zoster (chicken pox) in the dorsal root ganglion

© Elsevier 2005

CMV
Cytomegalovirus

- Particularly important in fetal/neonate population - TORCH
- Common opportunistic infection in AIDS, affecting the CNS in 10-20% of cases
- Large intracytoplasmic and intranuclear inclusions
CSF Findings

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Fungal Diseases

- Can present as meningitis, encephalitis or brain abscess (rare in perinatal cases; found in pediatric transplant and hematopoietic malignancies)
- Cryptococcus is a common form of fungal meningitis (diagnosed by India Ink stain of CSF)
- Aspergillus or Candida most common via hematogenous route
- Zygomycetes (Mucor) usually direct spread from sinuses
References and Acknowledgments

1. Ellison and Love: Neuropathology 2c 2004 Elsevier LTD and Elsevier 2005
2. Kinney and Volpe (Volpe’s Neuropathology of Newborn 6th Ed)
3. Pediatric Neuropathology: A Text-Atlas Figures 2.7-3 and 2.7-5
5. A.Viaene Pediatric Neuropathology: Malformations AANP Teaching Rounds, Feb 24, 2021