

## Neuropathology and Placental Pathology of Acute Perinatal Asphyxia

Epidemiologic studies have implicated prenatal events involving hypoxic/ischemic and/or inflammatory/infectious injury as risk factors for neonatal brain damage and subsequent neurologic deficits (including cerebral palsy, seizures, mental retardation, hydrocephalus, learning and behavioral disorders, and SIDS). While epidemiologic studies provide statistical associations of various risk factors in a given population, examination of the placenta provides the unique opportunity to examine the record of an individual pregnancy. The literature concerning the usefulness of placental examination for neurologic prognosis is based in large part on the interpretations of experienced placental pathologists and case reports or small series of cases. The small numbers of controlled studies that exist are primarily retrospective analyses, a consequence of the relatively low frequency of poor neurologic outcome, particularly in term infants. With these limitations in mind, the following discussion reviews the brain lesions most frequently seen in perinatal autopsies and addresses placental factors associated with perinatal brain injury.

The most common forms of brain injury in the fetus/neonate fall into 3 categories:

- Germinal matrix hemorrhage
- White matter injury
- Neuronal injury (including infarcts and various patterns of selective neuronal injury).

These are often seen in combination, as illustrated by Skullerud & Westre (Skullerud, 1986).

### 96 preterm infants, <30 d survival

50% germinal matrix hemorrhage (GMH)

24% periventricular leukomalacia (PVL)

50% pontosubicular necrosis (PSN)

	PSN	PVL	PSN + PVL
+ GMH	40%	4%	31%
- GMH	35%	2%	10%

Other studies reporting the incidence of prenatal and perinatal brain damage: (Terplan, 1967; Gilles, 1983; Sims, 1985; Ellis, 1988; Squier, 1991; Gaffney, 1994; Grafe, 1994).

### **Germinal matrix hemorrhage (GMH):**

- Lesion of preterm infants (germinal matrix is a transient developmental tissue).
- Most occur < 3-4 d postnatal, some begin prenatally or intrapartum.

Pathophysiology of GMH:

- Hemodynamic disturbances.
  - Venous hemorrhage (increased venous pressure?) (Nakamura, 1991; Ghazi-Birry, 1997).
  - Lack of cerebral autoregulation (immaturity).
- Large lumen, thin-walled vessels with little supporting structures.

Pathology: single or multiple, unilateral or bilateral.

Radiologic grading system

Grade 1: In germinal matrix only

Grade 2: Extending into lateral ventricle

Grade 3: Filling and distending lateral ventricle

Grade 4: Extension into adjacent brain parenchyma

Long-term consequences include:

- Necrosis, then cyst formation
- Hydrocephalus
  - Obstruction of outflow of 4<sup>th</sup> ventricle (or occlusion of arachnoid villi) by arachnoid inflammation
  - Aqueductal stenosis due to clot or gliosis

White matter injury:

- Primarily a lesion of premature infants, but usually >26 weeks gestation (Leviton, 1984; Golden, 1997).
- Strongest correlation with cerebral palsy in preterm infants (Volpe, 2001).

Many terms have been used that in part describe the location and severity of injury.

White matter necrosis (WMN)

Periventricular leukomalacia (PVL) (Banker, 1962)

Periventricular infarcts

Subcortical leukomalacia

White matter gliosis

Perinatal telencephalic leukoencephalopathy (Gilles, 1969)

Pathology:

- Pallor and rarefaction
- Acutely injured glial cells
- Macrophages infiltration
- Reactive astrocytes
- Necrosis, cavitation, calcification
- Characteristic distribution in periventricular white matter

Theories of pathogenesis (selective vulnerability of white matter):

- Vascular border zone (proposed by van den Bergh, deReuck (Van den Bergh, 1969; DeReuck, 1972); contradicted by Kuban, Nelson (Kuban, 1985; Nelson, 1991).
- Lack of cerebral autoregulation.
- Increased metabolic demands of myelination (no).

- Development vulnerability of white matter cells (particularly oligodendrocytes) (Back, 2001).
- Intrauterine infection (Leviton, 1984).
  - Relationship to premature birth.
  - Direct effects on brain either by altering hemodynamics or causing direct cellular damage (endotoxin).
  - Effects of cytokines (TNF, interleukins).

### **Selective neuronal injury**

#### **Focal infarcts**

- MCA distribution
- Long term consequences
  - Porencephaly
  - Hydranencephaly
  - Polymicrogyria
  - Other abnormal cortical patterning at edge

#### **Other patterns of neuronal injury**

- Laminar necrosis
- Focal cortical necrosis in depths of sulci (ulegyria)
- Parasagittal injury
- Deep gray matter; cystic lesions, “status marmoratus”
- Pontosubicular necrosis
- Cerebellum
- Spinal cord or brainstem motor neurons

The appearance of acutely injured neurons can vary depending on gestational age, location in brain (developmental stage of specific neuronal populations), survival time, and the nature of the insult (single, acute, intermittent, chronic, on-going, effects of resuscitation).

**Placental factors** that have been associated with perinatal brain injury are primarily those that **either cause or reflect abnormalities of placental-fetal blood flow.**

- Placental and umbilical cord thrombi
- Villous infarcts
- Severe villous edema
- Meconium
- Monochorionic twinning
- Abruptio placentae
- Placental hemorrhages.

**Thrombi in the fetal vessels** of the placenta (chorionic surface and villous) and umbilical cord:

- May be either the result or cause of abnormal fetal-placental blood flow.
- Chorionic surface vessel thrombi correlate with brain injury in stillborn fetuses (Grafe, 1994).
- A high proportion of cases of cerebral palsy have thrombi in fetal vessels of the placenta (Kraus, 1997).

- Chorionic surface vessel thrombi associated with chorioamnionitis were associated with an increased risk of neurologic impairment at 20 months of age in very low-birthweight infants (Redline, 1998).
- Thrombi in the placental and cord veins have the potential to embolize, either prenatally or intrapartum, and produce focal cerebral infarcts (Kraus, 1999).
- Abnormal coagulation factors were increased in neonatal blood from children with cerebral palsy compared to neurologically normal controls (Nelson, 1998).

#### Causes of thrombi:

- Infection (chorioamnionitis, funisitis); endothelial damage, vasoconstriction.
- Meconium; vasoconstriction.
- Diabetic mothers (abnormal flow due to hyperviscosity?); congestion, increased nRBC's.
- Umbilical cord abnormalities: excessive length, excessive twisting, constrictions, velamentous insertion (abnormal flow).
- Maternal/fetal thrombophilic disorders?
- Specific etiology may not be apparent from gross or microscopic examination.

Thrombi can be reasonably “dated” histologically by the degree of organization.

The physiologic effect on the fetus is presumably influenced by the number, location and size of thrombi, all of which should be carefully considered in the placental examination.

#### Villous infarcts

- Multiple placental infarcts correlate with CNS ischemic changes in stillborns (Grafe, 1994; Burke, 1995) (by extrapolation also significant in liveborns?).
- Multiple placental infarcts were more frequent in neurologically impaired infants compared to controls, but not statistically significant (Redline, 1998).
  - But.....Signs of chronic ischemic changes (advanced villous maturation) were more frequent in controls than in neurologically impaired infants—could this represent ischemic “pre-conditioning”??

Evaluation of placentas with infarcts should include at a minimum the extent of placental involvement, locations of infarcts, and approximate age as determined histologically.

#### Severe villous edema

- Proposed as a cause of neurologic injury and other forms of neonatal morbidity by Naeye (Naeye, 1983; Naeye, 1992).
- Severe (but not mild) villous edema was increased in the placentas of infants with neurologic impairment (Redline, 1998).

#### Pathophysiology:

- Severe villous edema may compress the villous capillaries and directly interfere with placental-fetal blood flow.
- Villous edema may also be a correlate of other pathologic processes in the placenta and fetus.
- Endothelial injury (as in certain infections).

- Increased hydrostatic pressure (as with obstruction or increased venous pressure).
- Hydrops fetalis: 38 infants and fetuses with HF, 60% had hypoxic-ischemic brain injury (Larroche, 1992).

Villous edema is notoriously difficult to grade and may be affected by:

- Time from delivery to fixation.
- Storage conditions.

### **Meconium**

Meconium staining of the amniotic fluid or placenta has been associated with an increased risk for cerebral palsy in preterm infants (Spinillo, 1997a; Spinillo, 1997b) and with white matter damage in stillborns (Grafe, 1994).

### **Proposed pathophysiology**

- Vasoconstriction and subsequent necrosis of the vessels of the chorionic plate and umbilical cord (Altshuler, 1989; Sienko, 1999).

The association between meconium and neurologic damage may also reflect the release of meconium as a response to injury; cause and effect may vary with different clinical situations.

- The timing of meconium release relative to delivery is often considered an important line of argument in the medicolegal setting.
- How long does it take for meconium-laden macrophages to pass through the amnion to the chorion and then to the decidua? through Wharton's jelly in the umbilical cord?
  - In vivo studies defining the time course of this process do not exist.
  - Co-existing processes (infection) may likely alter the time course of this reaction.

### **Twins**

- Monochorionic twins are at increased risk for prenatal brain injury (Grether, 1993).
- Case reports and small series in which one twin has died in utero and the surviving twin has subsequent brain damage (Benirschke, 1961; Moore, 1969; Smith, 1975; Yoshioka, 1979; Rolland, 1983; Sherer, 1993).
- Antenatal brain damage is more frequent in monochorionic twins with placental vein-vein or artery-artery anastomoses (Bejar, 1990).

### **Pathophysiology**

- Blood pressure instability in the setting of direct artery-artery or vein-vein anastomoses in the placental circulations.
  - Dead twin becomes a venous "sink," blood flows from the living twin into the dead twin and the living twin experiences profound hypotension (Larroche, 1990; Benirschke, 1992; 1993).
  - Can occur even without the death of one twin (Bejar, 1990), (Larroche, 1990).

Include in the evaluation of a twin placenta:

- Presence or absence of chorionic surface vascular anastomoses.
- Type of vessels involved (arteries or veins), size, number, direction of A-V shunts.

A thorough guide for the examination of multiple gestation placentas was published by Baldwin (Baldwin, 1994). Other texts of placental or perinatal pathology also give appropriate guidelines.

### **Acute hemorrhagic events (acute hypotension/hypoperfusion)**

Abruptio placentae

Hemorrhage due to rupture of velamentous vessels or torn cord insertions

Intraplacental hemorrhage

- Three-fold increased risk for WMN in infants with abruptio placentae (Gibbs, 1994).
- Abruptio placentae is a clinical event that should be recognized by the delivering practitioner and only confirmed by the pathologist.

Pathologic correlates include retroplacental clot (with compression of the underlying placenta) and torn vessels.

- Partial, old abruptio (occurring days to weeks before delivery) or intraplacental hemorrhage may not be apparent clinically; placental examination can document these changes and their approximate time frame.
- Increased numbers of nucleated RBC can indicate a fetal response to loss of blood volume and can also be seen with anoxia, anemia and maternal diabetes. This response takes time (hours) to develop and will not be seen immediately following blood loss or hypoxia.

### **Infection: Chorioamnionitis**

The relationship between chorioamnionitis and neonatal encephalopathy is complex and probably compound. There can be both direct effects (infection of the fetus/newborn) and indirect effects (cytokine release, vascular responses, meconium release, prematurity).

May thus interact with multiple placental factors described above.

Epidemiologic associations between chorioamnionitis (Leviton, 1973; Leviton, 1976; Nelson, 1986; Grether, 1997) and neonatal encephalopathy or cerebral palsy have prompted much speculation as to possible pathophysiologic mechanisms.

- Histologic chorioamnionitis also does not always correlate with clinical chorioamnionitis.
- Grether and Nelson (Grether, 1997) found a nine-fold risk for cerebral palsy in pregnancies with either a clinical or histologic diagnosis of chorioamnionitis.
- Prenatal brain damage (WMN or GMH) has been reported to be associated with histologic chorioamnionitis and funisitis (Bejar, 1988; Cooke, 1990; Grafe, 1994).
- In low birthweight infants, clinical chorioamnionitis, but not histologic chorioamnionitis, correlated with the presence of periventricular white matter injury and IVH (Verma, 1997).
- Histologic chorioamnionitis correlated with clinical chorioamnionitis only when there was a fetal vascular response (Redline, 2000).
- The risk for neurologic impairment in infants with chorioamnionitis could be accounted for by the presence of chorionic surface vessel thrombi (Redline, 1998; 2000).
- Yoon (Yoon, 2000) found that the presence of funisitis (fetal inflammatory response) was a risk factor for cerebral palsy and white matter damage.

### Pathologic interpretation of chorioamnionitis

Chorioamnionitis is a highly variable process.

- Different organisms produce markedly different physiologic and histologic responses in the placental and fetus (e.g Group B strep).
- The etiologic agent for histologically identified chorioamnionitis is frequently not known (cultures often not performed).
- Variations in host response to different organisms.
- The presence of other factors such as meconium.

These factors may result in dilution of effect in studies that consider chorioamnionitis as a single entity. Since histologic chorioamnionitis is so common, a detailed subclassification of chorioamnionitis may be necessary to define those infants at risk for neurologic impairment.

### **Infection: Villitis**

The relationship between villitis and neonatal encephalopathy is even less clear.

Etiology is often never determined (cultures often not performed).

Villitis is often seen in asymptomatic mothers.

Cytomegalovirus (CMV).

Intrauterine infection with CMV can result in destructive brain lesions and serious neurologic sequelae. A careful search for the signs of CMV infection in the villi such as viral inclusions, plasma cells, vascular sclerosis and hemosiderin is warranted in all cases of villitis. The value of ancillary tests on placental tissue such as immunohistochemistry or in situ hybridization in cases where none of these features are present is uncertain.

A variable further confounding the relationship between chorioamnionitis and neonatal encephalopathy is the association between chorioamnionitis and prematurity. This association has been discussed in numerous forums and will not be further addressed here. The increased risk for developing cerebral palsy in very preterm and very low birthweight infants is well established. Developmental age at the time of an insult or injury is extremely important when considering the potential effects of perinatal brain injury. The sensitivity to hypoxic-ischemic injury and the cellular response to this injury are known to change during development. When exposed to hypoxia or ischemia, the developmental states of neurons (and their connections with other neurons), oligodendrocytes (and their role in myelination) and microglia/macrophages (and the production of cytokines) are all likely to affect the sensitivity of the brain to injury. The contribution of the inflammatory response to the final damage is also likely to change with development. These factors may interact to result in the changing “selective vulnerability” or resistance of the brain to hypoxic-ischemic injury during development.

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