Birth Asphyxia (Hypoxia-Ischemia)

Anoxia is a term used to indicate the consequences of complete lack of oxygen as a result of a number of primary causes. **Hypoxia** refers to decreased arterial concentration of oxygen. **Ischemia** refers to blood flow to cells or organs that is insuffi-cient to maintain their normal function. Hypoxic-ischemic encephalopathy is an important cause of permanent damage to CNS tissues that may result in neonatal death or manifest later as cerebral palsy or developmental delay. Fifteen to 20% of infants with hypoxic-ischemic encephalopathy (HIE) die in the neonatal period, and 25–30% of survivors are left with permanent neurodevelopmental abnormalities (cerebral palsy, mental retardation). The greatest risk of adverse outcome is seen in infants with fetal acidosis (pH <7.0), a 5-min Apgar score of 0–3, hypoxic-ischemic encephalopathy (altered tone, depressed level of consciousness, seizures), and other multiorgan system signs.

TABLE 99-2 -- Multiorgan Systemic Effects of Asphyxia

SYSTEM	EFFECT
Central nervous system	Hypoxic-ischemic encephalopathy, infarction, intracranial hemorrhage, seizures, cerebral edema, hypotonia, hypertonia
Cardiovascular	Myocardial ischemia, poor contractility, cardiac stun, tricuspid insufficiency, hypotension
Pulmonary	Pulmonary hypertension, pulmonary hemorrhage, respiratory distress syndrome
Renal	Acute tubular or cortical necrosis
Adrenal	Adrenal hemorrhage
Gastrointestinal	Perforation, ulceration with hemorrhage, necrosis
Metabolic	Inappropriate secretion of antidiuretic hormone, hyponatremia, hypoglycemia, hypocalcemia, myoglobinuria
Integument	Subcutaneous fat necrosis
Hematology	Disseminated intravascular coagulation

ETIOLOGY.

Most neonatal encephalopathic or seizure disorders, in the absence of major congenital malformations or syndromes, appear to be due to perinatal events rather than prenatal events. Brain MRI or autopsy findings of full-term neonates with encephalopathy demonstrated that 80% have acute injuries, <1% have prenatal injuries, and 3% have non-hypoxic ischemic diagnoses. Fetal hypoxia may be caused by various disorders in the mother, including (1) inadequate oxygenation of maternal blood from hypoventilation during anesthesia, cyanotic heart disease, respiratory failure, or carbon monoxide poisoning; (2) low maternal blood pressure from acute blood loss, spinal anesthesia, or compression of the vena cava and aorta by the gravid uterus; (3) inadequate relaxation of the uterus to permit placental filling as a result of uterine tetany caused by the administration of excessive oxytocin; (4) premature

separation of the placenta; (5) impedance to the circulation of blood through the umbilical cord as a result of compression or knotting of the cord; and (6) placental insufficiency from toxemia or postmaturity.

Placental insufficiency often remains undetected on clinical assessment. Intrauterine growth restriction may develop in chronically hypoxic fetuses without the traditional signs of fetal distress. Doppler umbilical waveform velocimetry (demonstrating increased fetal vascular resistance) and cordocentesis (demonstrating fetal hypoxia and lactic acidosis) identify a chronically hypoxic infant (Chapter 96). Uterine contractions may further reduce umbilical oxygenation and depress the fetal cardiovascular system and CNS and result in low Apgar scores and postnatal hypoxia in the delivery room.

After birth, hypoxia may be caused by (1) failure of oxygenation as a result of severe forms of cyanotic congenital heart disease or severe pulmonary disease; (2) anemia severe enough to lower the oxygen content of the blood (severe hemorrhage, hemolytic disease); (3) shock severe enough to interfere with the transport of oxygen to vital organs from overwhelming sepsis, massive blood loss, and intracranial or adrenal hemorrhage.

PATHOPHYSIOLOGY AND PATHOLOGY.

The pathology of hypoxia-ischemia is dependent on the affected organ and the severity of the injury. Early congestion, fluid leak from increased capillary permeability, and endothelial cell swelling may then lead to signs of coagulation necrosis and cell death. Congestion and petechiae are seen in the pericardium, pleura, thymus, heart, adrenals, and meninges. Prolonged intrauterine hypoxia may result in inadequate perfusion of the periventricular white matter, resulting, in turn, in PVL. Pulmonary arteriole smooth muscle hyperplasia may develop, which predisposes the infant to pulmonary hypertension (Chapter 101.8). If fetal distress produces gasping, the amniotic fluid contents (meconium, squames, lanugo) are aspirated into the trachea or lungs.

The combination of chronic fetal hypoxia and acute hypoxic-ischemic injury after birth results in gestational age-specific neuropathology (Table 99-3). Term infants demonstrate neuronal necrosis of the cortex (later, cortical atrophy) and parasagittal ischemic injury. Preterm infants demonstrate PVL (later, spastic diplegia), status marmoratus of the basal ganglia, and IVH. Term more often than preterm infants have focal or multifocal cortical infarcts that clinically manifest as focal seizures and hemiplegia.

CLINICAL MANIFESTATIONS.

Intrauterine growth restriction with increased vascular resistance may be the 1st indication of fetal hypoxia. During labor, the fetal heart rate slows, and beat-to-beat variability declines. Continuous heart rate recording may reveal a variable or late (type II) deceleration pattern (see Fig. 96-4), and fetal scalp blood analysis may show a pH <7.20 (Chapter 96). The acidosis usually has both metabolic and respiratory components. Particularly in infants near term, these signs should lead to the

administration of high concentrations of oxygen to the mother and immediate delivery to avoid fetal death or CNS damage.

At delivery, the presence of yellow, meconium-stained amniotic fluid is evidence that fetal distress has occurred. At birth, these infants are frequently depressed and fail to breathe spontaneously. During the ensuing hours, they may remain hypotonic or change from hypotonic to hypertonic, or their tone may appear normal (Table 99-4). Pallor, cyanosis, apnea, a slow heart rate, and unresponsiveness to stimulation are also signs of hypoxic-ischemic encephalopathy. Cerebral edema may develop during the next 24 hr and result in profound brainstem depression. During this time, seizure activity may occur; it may be severe and refractory to the usual doses of anticonvulsants. Phenobarbital, the drug of choice, is given with an intravenous loading dose (20 mg/kg); additional doses of 5–10 mg/kg (up to 40–50 mg/kg total) may be needed. Phenytoin (20 mg/kg loading dose) or lorazepam (0.1 mg/kg) may be needed for refractory seizures. Phenobarbital levels should be monitored 24 hr after the loading dose and maintenance therapy (5 mg/kg/24 hr) are begun. Therapeutic phenobarbital levels are 20–40 μg/mL. Though most often a result of the hypoxic-ischemic encephalopathy, seizures in asphyxiated newborns may also be due to hypocalcemia, hypoglycemia, or infection.

TABLE 99-4 -- Hypoxic-Ischemic Encephalopathy in Term Infants

SIGNS	STAGE 1	STAGE 2	STAGE 3
Level of consciousness	Hyperalert	Lethargic	Stuporous, coma
Muscle tone	Normal	Hypotonic	Flaccid
Posture	Normal	Flexion	Decerebrate
Tendon reflexes/clonus	Hyperactive	Hyperactive	Absent
Myoclonus	Present	Present	Absent
Moro reflex	Strong	Weak	Absent
Pupils	Mydriasis	Miosis	Unequal, poor light reflex
Seizures	None	Common	Decerebration
Electroencephalographic	Normal	Low voltage changing to seizure activity	Burst suppression to isoelectric
Duration	<24 hr if progresses; otherwise, may remain normal	24 hr to 14 days	Days to weeks
Outcome	Good	Variable	Death, severe deficits

In addition to CNS dysfunction, heart failure and cardiogenic shock, persistent pulmonary hypertension, respiratory distress syndrome, gastrointestinal perforation,

hematuria, and acute tubular necrosis are associated with perinatal asphyxia secondary to inadequate perfusion (see Table 99-2).

After delivery, hypoxia is due to respiratory failure and circulatory insufficiency. The severity of neonatal encephalopathy depends on the duration and timing of injury. Symptoms develop over a series of days, making it important to perform serial neurological examinations (see Table 99-4). During the initial hours after an insult, infants have a depressed level of consciousness. Periodic breathing with apnea or bradycardia is present, but cranial nerve functions are often spared with intact pupillary responses and spontaneous eye movement. Seizures are common with extensive injury. Hypotonia is also common as an early manifestation.

DIAGNOSIS.

Ultrasound has limited utility in evaluation of hypoxic injury in the term infant; it is the preferred modality in evaluation of the preterm infant. CT scans are helpful in identification of focal hemorrhagic lesions, diffuse cortical injury, and damage to the basal ganglia; CT has limited ability to identify cortical injury within the 1st few days of life. Diffusion-weighed MRI is the preferred imaging modality because of its increased sensitivity and specificity early in the process and its ability to outline the topography of the lesion.

TREATMENT.

Systemic or selective cerebral hypothermia for the acute management of HIE is promising because it may decrease the rate of apoptosis and suppresses production of mediators known to be neurotoxic, including extracellular glutamate, free radicals, NO, and lactate. The neuroprotective effects are thought to be secondary to downregulating the secondary mediators of injury resulting from cerebral edema, accumulation of cytokines, and seizures. Animal data suggest that the intervention is most effective when implemented within 6 hr of the event.

Several trials demonstrated that either isolated cerebral cooling or whole body hypothermia are safe and well tolerated by term or near-term infants with HIE. Systemic hypothermia may result in more uniform cooling of the brain and deeper CNS structures. Infants treated with systemic hypothermia have a lower incidence of cortical neuronal injury on MRI. Early small clinical trials demonstrated no significant adverse short-term effects and a trend toward improved neurodevelopmental outcome at 18 mo among infants with moderate to severe encephalopathy. Selective head cooling is not effective in infants with the most severe aEEG findings, but is effective in those with less severe aEEG changes.

Additional therapy for infants with HIE includes supportive care directed at management of organ system dysfunction. Careful attention to ventilatory status and adequate oxygenation, blood pressure, hemodynamic status, acid-base balance, and possible infection is important. Secondary hypoxia or hypotension due to complications of HIE must be prevented. Aggressive treatment of seizures is critical and may necessitate continuous electroencephalographic monitoring.

PROGNOSIS.

The outcome of HIE correlates to the timing and severity of the insult and ranges from complete recovery to death. The prognosis varies depending on whether the metabolic and cardiopulmonary complications (hypoxia, hypoglycemia, shock) are treated, the infant's gestational age (outcome is poorest if the infant is preterm), and the severity of the encephalopathy. Severe encephalopathy (see Table 99-4), characterized by flaccid coma, apnea, absent oculocephalic reflexes, and refractory seizures, is associated with a poor prognosis. A low Apgar score at 20 min, absence of spontaneous respirations at 20 min of age, and persistence of abnormal neurologic signs at 2 wk of age also predict death or severe cognitive and motor deficits. The combined use of an early electroencephalogram (EEG) and MRI is useful in predicting outcome in term infants with HIE. Normal MRI and EEG findings are associated with a good recovery, whereas severe MRI and EEG abnormalities predict a poor outcome. Infants with stage 2 and 3 encephalopathy are at the highest risk for adverse outcome. Microcephaly and poor head growth during the 1st year of life also correlate with injury to the basal ganglia and white matter and adverse developmental outcome at 12 mo. All survivors of moderate to severe encephalopathy require comprehensive high-risk medical and developmental follow-up. Early identification of neurodevelopmental problems allows prompt referral for developmental, rehabilitative, neurologic care, and early intervention services so that the best possible outcome can be achieved.