Neurological Complications of Perinatal Asphyxia

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The degree of asphyxia is best ascertained by measuring the amount of fetal acidosis determined by umbilical arterial blood. An umbilical arterial pH of less than 7.0 is seen in about 0.3% of deliveries. It indicates a severity of acidosis that places the fetus at risk for permanent neurological damage because of asphyxia. However, the outcome of infants with umbilical cord pH of less than 7.0 who required neonatal intensive care is relatively good. Eighty-one percent can be expected have a normal examination at discharge.

Asphyxia refers to impairment in the exchange of respiratory gases, oxygen, and carbon dioxide coupled with hypercapnia and consequent acidosis and changes in cerebral blood flow. The clinical correlates of this pathophysiological definition of asphyxia have been the topic of numerous studies but, as yet, there is no true consensus.

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This relative resistance of the brain to asphyxia is probably the consequence of a variety of fetal mechanisms that adapt to lack of oxygen and reduced cerebral blood flow. Also note that umbilical artery acidemia at birth is not invariably present in infants born with acute birth asphyxia.

A number of other clinical and laboratory signs and symptoms suggest the presence of asphyxia. Alterations in fetal heart rate pattern have been studied as a diagnostic marker. Valentin and colleagues demonstrated that the most abnormal cord arterial pHs were associated with a pattern of reduced variability, reduced variability with late decelerations, or bradycardia with late decelerations. The passage of meconium and the presence of meconium-stained amniotic fluid also have been shown to indicate fetal distress and have been associated with fetal hypoxia, acidosis, and asphyxia. In the past, it was thought that a low Apgar score suggested asphyxia, but this has been debunked. Numerous studies have found low Apgar scores in infants with normal cord arterial pH and normal Apgar scores in asphyxiated infants.

Umbilical cord lactate and serum concentrations of neuron-specific enolase have been suggested as markers for perinatal asphyxia and as an indication of the severity of hypoxic ischemic encephalopathy. These tests have not yet been found to have widespread clinical applicability. An abnormal neonatal course that includes features such as delayed or impaired respiration requiring resuscitative measures, a prolonged depressed Apgar score, seizures, hypotonia, and a bulging fontanel is the most important clue to the presence of perinatal asphyxia of sufficient severity to cause neurological deficits. Less obvious abnormalities are irritability, feeding difficulties, excessive jitters, or an abnormal cry.

In addition, clinical or laboratory evidence for asphyxial damage to organs other than the brain may be present. The multiple-organ dysfunction phenomenon is related to the diving reflex. This reflex, activated by asphyxia, consists in shunting blood from the skin and splanchnic area to the heart, adrenals, and brain, ostensibly to protect these vital organs from hypoxic-ischemic injury. In the series by Shah and colleagues, infants who had asphyxia injury to the brain showed evidence of dysfunction in at least 1 other organ.

The infant whose birth was complicated but whose neonatal period was uneventful is not at increased risk for neurological damage. The absence of the noted signs and symptoms in a youngster who subsequently presents with cerebral palsy points to a cause other than perinatal asphyxia.

Increased amounts of nucleated red blood cells (nRBCs) are frequently recorded in the infant with acute, subacute, or chronic asphyxia. There is a large overlap between nRBC values after acute and chronic asphyxia, however. Asphyxia of any duration does not invariably cause an increased nRBC
count, and extreme increases can be found in the absence of asphyxia. Because cerebrospinal fluid (CSF) protein may be elevated after perinatal asphyxia, examination of CSF can provide some diagnostic evidence. In the term neonate, the mean CSF protein concentration is 90 mg/dL; values of more than 150 mg/dL are considered abnormal. In the premature neonate, the mean CSF protein concentration is 115 mg/dL. The presence of blood from any source raises the total protein by 1.5 mg/dL of fluid for every 1000 fresh red blood cells/µL. An elevation in the ratio of CSF lactate to pyruvate as well as a striking elevation of blood creatine kinase-BB isoenzyme persists in asphyxiated infants for several hours after normal oxygenation has been reestablished. However, a normal CSF does not exclude the possibility of perinatal asphyxia.

Neuroimaging studies are the best way to define the extent of asphyxial injury and to differentiate asphyxial injury from developmental or other acquired abnormalities. Ultrasonography, although easily performed, is of somewhat limited value in the evaluation of the asphyxiated infant. Although CT is useful for the detection of hemorrhage, difficulties are encountered in the CT analysis of parenchymal changes, and MRI is therefore the preferred imaging tool for delineating the extent and nature of asphyxial damage in the clinically stable term infant.

MRI performed on asphyxiated infants within the first 10 days of life demonstrates 3 patterns of damage. In one pattern seen in term infants, abnormalities are most commonly confined to the thalamus and basal ganglia. In one study, almost all infants with these lesions suffered an acute profound asphyxial insult. Mercuri and colleagues noted a stronger association between Apgar scores and basal ganglia lesions than with cord pH.

In another pattern, abnormalities are predominantly in the cerebral cortex and subcortical white matter. Periventricular white matter abnormalities are generally seen in preterm infants or in infants believed to have sustained in utero asphyxial damage before 34 to 35 weeks' gestation. Brainstem and cerebellar abnormalities are less common. In the series by Sie and coworkers, 26% of infants who demonstrated periventricular leukomalacia (PVL) on MRI were born at term. In some infants, a mixed pattern of abnormalities, indicated via imaging studies, is seen. Contrast enhancement of abnormalities in the thalamus and basal ganglia in particular correlates with tissue necrosis and, thus, predicts a poor outcome.

Focal parenchymal hemorrhages, mainly in a parietal or parieto-occipital distribution, were common in the series by Keeney and colleagues. These were unilateral or bilateral and generally resolved to be replaced by atrophy, thinning of myelin, or hemosiderin deposition. Basal ganglia hemorrhage can be seen in a small proportion of asphyxiated infants. The hemorrhage can resolve or become cystic or calcified. For reasons as yet unknown, calcification can appear as early as 2 weeks after the asphyxial insult. After perinatal asphyxia, there is a delay in myelination. This is best identified after 7 to 8 months of age.

The abnormalities observed with neonatal brain imaging are even better delineated in neuropathological studies. These studies demonstrate a highly selective vulnerability of certain neuronal populations to perinatal asphyxia. When the primate fetus is subjected to acute total asphyxia, a reproducible pattern of brain disorders ensues. This pattern includes bilaterally symmetrical lesions in the thalamus and in a number of brainstem nuclei, notably the nuclei of the inferior colliculus, superior olive, and lateral lemniscus. The neurons of the cerebral cortex, particularly the hippocampus, are especially vulnerable, as are the Purkinje cells of the cerebellum. Factors that determine this phenomenon are incompletely understood. In part, the regional distribution of injury reflects the vascular supply to the brain. Injury is maximal in the border zones between the major cerebral arteries. In the striatum, the topography of neuronal death is probably related to the density of excitatory receptors and the expression of the various receptor subtypes.

Inflammatory reactions involving a variety of cytokines also may contribute to hypoxic-ischemic cell death. The increase in cytokines could stem from an infection, notably achorioamnionitis that predates the hypoxic-ischemic insult, or it could result from activation of microglia by asphyxia. The relative frequency of prenatal and perinatal lesions verified by pathological studies is illustrated in Table 1.
<table>
<thead>
<tr>
<th>Category</th>
<th>Total (Number)</th>
</tr>
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<tbody>
<tr>
<td>Prenatal</td>
<td>150 (50.5)</td>
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<tr>
<td>Malformations</td>
<td>93 (31.3)</td>
</tr>
<tr>
<td>Chiari syndromes</td>
<td>23</td>
</tr>
<tr>
<td>Microgyria, pachygyria</td>
<td>18</td>
</tr>
<tr>
<td>Primary microcephaly</td>
<td>9</td>
</tr>
<tr>
<td>Agenesis of corpus callosum</td>
<td>8</td>
</tr>
<tr>
<td>Ectopic gray matter</td>
<td>6</td>
</tr>
<tr>
<td>Abnormal convolutional pattern</td>
<td>6</td>
</tr>
<tr>
<td>Other malformations</td>
<td>23</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>31 (10.4)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>23 (7.7)</td>
</tr>
<tr>
<td>Prenatal infections</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Unclassified</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Perinatal</td>
<td>47 (15.8)</td>
</tr>
<tr>
<td>Circulatory lesions</td>
<td>42 (14.1)</td>
</tr>
<tr>
<td>Mechanical birth trauma</td>
<td>5 (1.7)</td>
</tr>
<tr>
<td>Postnatal (genetic disorders, leukodystrophies, lipidoses)</td>
<td>27 (9.1)</td>
</tr>
<tr>
<td>Postnatal (meningitis, encephalitis)</td>
<td>44 (14.8)</td>
</tr>
<tr>
<td>Unknown (whether perinatal or prenatal)</td>
<td>29 (9.8)</td>
</tr>
</tbody>
</table>

*No morphological lesions were detectable in 62 other autopsies.*
Neuropathological Lesions

**Parasagittal cerebral injury.** The most common site of brain damage in the term newborn is the cortex. Experimental studies have confirmed that the parasagittal cortex is the earliest and most severely damaged in prolonged asphyxia, with the amount of damage increasing geometrically with increasing duration of asphyxia.

The lesions characteristically involve the territory supplied by the most peripheral branches of the 3 large cerebral arteries. Infarctions in this area are secondary to arterial or venous stasis and thromboses.

One common pattern for the distribution of lesions, termed arterial "border zone" or "watershed lesions," usually results from a sudden decrease in systolic blood pressure and cerebral perfusion. The best-known watershed lesions in the brain are between the anterior and middle cerebral artery circulations and between the middle and posterior cerebral circulations. Another watershed zone occurs in the tegmentum of the brainstem between the territories of the paramedian penetrating the long circumferential arteries.

Watershed zone infarcts in the full-term neonatal cerebrum are usually ischemic. In about 30% of cases, they are hemorrhagic. In pre-term infants, hemorrhagic watershed infarcts are more frequent than ischemic infarcts.

The lesions may be located in the cortex or white matter. When gray matter is affected, damage usually involves the portions around the depth of the sulci. In part, this distribution can reflect the effect of cerebral edema on the drainage of the cortical veins, and, in part, it can be the consequence of the impoverished vascular supply of this area in the healthy newborn.

Lesions involving damage to the deeper portions of gray matter have been termed "ulegyria" (mantle sclerosis, lobar sclerosis, and nodular cortical sclerosis). Ulegyria accounts for approximately a third of clinical defects caused by circulatory disorders during the neonatal period.

Its characteristic feature is the localized destruction of the lower parts of the wall of the convolution, with relative sparing of the crown. This produces a "mushroom" gyrus.

Ulegyria can be extensive or so restricted that the gross appearance of the brain is normal. When ulegyria is widespread, an associated cystic defect in the subcortical white matter (porencephalic cyst) and dilatation of the lateral ventricles often occur. The meninges overlying the affected area are thickened, and the small arteries occasionally show calcifications in the elastica. Less often, ulegyria involves the cerebellum.

Marin-Padilla has studied the postinjury gray matter alterations in ulegyria and found that the surviving cortex acquires a cortical dysplasia that affects the structural and functional differentiation of neurons, glial elements and synaptic organization. Marin-Padilla proposed that the consequences of the acquired cortical dysplasia represent the main pathogenetic mechanism for epilepsy and other neurological sequelae to perinatal brain damage.

Selective neuronal necrosis and laminar necrosis of the cortex. The distribution of cerebral lesions induced by acute total asphyxia rarely reproduces the distribution of lesions found in infants who have survived partial but prolonged asphyxia. When prolonged partial asphyxia is induced experimentally, primates develop high carbon dioxide partial pressure levels and mixed metabolic and respiratory acidosis. These changes are usually accompanied by marked brain swelling, which compresses the small blood vessels of the cerebral parenchyma.

The resultant increase in vascular resistance superimposed on the systemic alterations leads to various focal cerebral circulatory lesions, the location of which is governed in part by vascular patterns and in part by the gestational age of the fetus at the time of the asphyxial insult. Selective necrosis of neurons may be followed by the mineralization of those cells.

The neonatal cerebral cortex is vulnerable to laminar necrosis after a severe ischemic insult. Laminar necrosis may be identified on MRI, particularly in fluid-attenuated inversion recovery sequences, as a bright line of increased signal within the cortex and parallel to the surface of the brain.

**PVL.** PVL occurs with particular frequency in the premature infant. This lesion consists of a bilateral, fairly symmetrical necrosis that has a periventricular distribution. The 2 most common sites of occurrence are at the level of the occipital radiation and in the white matter around the foramen of Monro. In addition, diffuse cerebral white matter necrosis that usually spares the gyral cores may develop.

The pathogenesis of PVL is most likely multifactorial. Major factors are listed in Table 2.

<table>
<thead>
<tr>
<th>Table 2— Major pathogenic factors in PVL</th>
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Failure regarding perfusion of the periventricular region accompanied by impairment of cerebral vascular autoregulation, with a propensity for pressure-passive circulation.

Intrinsic vulnerability of early differentiating oligodendroglia to excitatory neurotransmitters, such as glutamate.

Intrinsic vulnerability of early differentiating oligodendroglia to attack by free radicals.

Hypocarbia induced by mechanical ventilation.

The presence of elevated cytokine levels.

PVL, periventricular leukomalacia.

The role of cytokines in the evolution of PVL has received considerable attention recently. It appears likely that cytokines such as interferon-α, interferon-γ, tumor necrosis factor α, interleukin (IL)-6, and IL-8 might damage white matter by causing hypotension or by inducing ischemia through intravascular coagulation. Cytokines also could have a direct adverse effect on developing oligodendroglia or inducing the production of other cytokines, such as platelet-activating factor, which can further damage cells. The contribution of perinatal and prenatal asphyxia to the evolution of PVL has been reviewed by Folkerth.

From a clinical point of view, spastic diplegia is the most common and most consistent sequela of PVL. It is nearly always bilateral, although often asymmetrical in severity. Because of the propensity of the periventricular necrotizing lesions to appear earliest and most prominently around the occipital horns of the lateral ventricles, optic radiation fibers may be involved, and this sometimes also results in cortical visual impairment.

A number of adverse clinical perinatal events correlate with the development of PVL. In one study, the highest incidence was seen in infants aged 24 to 26 weeks. Notable prenatal risk factors include premature, prolonged, or both premature and prolonged rupture of membranes; chorioamnionitis; and intrauterine infections.

In many instances, however, infants affected by PVL have a relatively benign postnatal course. As a rule, the less mature the periventricular vasculature, the less significant the clinical complications that accompany the evolution of PVL.

Multicystic encephalomalacia. The neonatal brain responds to infarction differently than the mature brain. Rather than forming dense gliotic scars, the usual long-term residual lesions are pseudocysts. One of the reasons that cysts form is because areas of infarction tend to be larger in the newborn brain than in the adult brain; collateral circulation is less developed. Another reason is that the ability of neonatal brain to mobilize reactive gliosis is limited.

When small, the cysts are trabeculated and do not communicate with the ventricular system. In their most extensive form, they can involve both hemispheres, leaving only small remnants of cortical tissue. This pathological picture is seen not only as a consequence of severe perinatal asphyxia but also in twin pregnancies after intrauterine fetal death and in fetal viral encephalitides, such as herpes simplex infection. A severe form of spastic quadriplegia usually develops in infants with this pathological picture.

Abnormalities of basal ganglia. Abnormalities within the basal ganglia develop in as many as 84% of
patients in whom perinatal asphyxia occurs. One common lesion seen in this area has been termed "status marmoratus." Fundamentally, the pathological picture is one of glial scarring corresponding to the areas of tissue destruction. It is characterized by a gross shrinkage of the striatum, particularly the globus pallidus, associated with hypermyelination and demyelination, which probably represent different responses to the same insult. Although the abnormalities within the basal ganglia are often the most striking, a variety of associated cortical lesions can be detected in most instances.

It has been our experience and that of others that this condition is the result of an acute, severe hypoxic insult. As a rule, the asphyxia is not as prolonged as it is in multicystic encephalomalacia, a condition in which there is also extensive damage to the cerebral cortex and white matter. The reasons for the selective vulnerability of the basal ganglia to asphyxia have not been fully clarified. Given that the basal ganglia have a higher baseline oxygen consumption than other regions of the brain, other factors also must be operative to account for the particular vulnerability of the putamen and anterior thalamus. The current thinking is that the topography of neuronal death points to a primary role of glutamate excitotoxicity in basal ganglia neuronal damage, with the type of cell death induced by asphyxia (necrosis or apoptosis) being determined by neuronal maturity and the severity and duration of asphyxia. In regions containing large amounts of apoptosis inhibitors, necrosis predominates; conversely, in the absence of endogenous apoptosis inhibitors hypoxia-ischemia induces apoptosis. Also playing a role is the density of excitatory receptors, the differential expression of ionotropic and metabotropic glutamate receptors, their differential sensitivities, and the expression of various receptor subtypes.

Abnormalities of cerebellum, brainstem, and pons. Occasionally, the major structural alterations resulting from perinatal injury are localized to the cerebellum. In most instances, the involvement is diffuse, with widespread disappearance of the cellular elements of the cerebellar cortex, notably the Purkinje cells, and the dentate nucleus. As is the case with the periventricular germinal matrix around the lateral ventricles, the external granular layer of the cerebellum is vulnerable to spontaneous hemorrhage, especially in preterm infants of young gestational age. However, in the vast majority of infants, selective cerebellar involvement is not the consequence of asphyxia. In general, the human neonatal brainstem appears to be more resistant to ischemic and hypoxic insults than the cerebral cortex, but it is not invulnerable, and sometimes lesions are more prominent in the brainstem than in supratentorial structures. The lesions are usually symmetrical and involve both gray matter nuclei and adjacent white matter tracts, but the gray matter is more focally involved, perhaps because of its higher metabolic rate.

Lesions may involve the inferior or superior colliculus almost selectively, or infarction may occur in the central core of the brainstem or selectively in the periaqueductal gray matter. Bilateral tegmental infarcts of the pons and medulla oblongata in particular are frequent sequelae of transient fetal hypotension because, as already mentioned, the tegmentum is a watershed zone. Because many of the deep infarcts are microscopic, particularly those of the brainstem, they are difficult to identify on neuroimaging.

Involvement of the nucleus ambiguus, which is ventrolateral to the tractus solitarius, can result in dysphagia because this nucleus provides motor neurons for the muscles of deglutition. Involvement of the trigeminal motor nucleus by tegmental infarcts may damage motor neurons to the masticatory muscles, such as the masseter and pterygoids. Pontosubicular degeneration. Pontosubicular degeneration in isolation or accompanied by widespread cerebral damage has been described in premature and term infants. It is not a rare entity; however, its pathogenesis is poorly understood, and the role perinatal asphyxia plays in its cause has not been well studied.

The condition represents a unique topology of pathological neuronal apoptosis in the fetal and neonatal brain, following hypoxia or ischemia. As its name implies, it selectively involves relay nuclei of the corticopontocerebellar pathway in the basis pontis and the subiculum, a transitional cortex between the 3-layered hippocampus and the 6-layered hippocampal gyrus. Although it may coexist with other hypoxic lesions in the cortex, thalamus, and cerebellum, these other regions are disproportionately less severely involved than the pontine nuclei and subiculum. This distribution of infarcts is generally seen in infants older than 29 weeks' gestation, most commonly in infants of 32 to 36 weeks' gestation. Pontosubicular degeneration is not better recognized by clinicians because it is difficult to demonstrate during life and remains essentially a postmortem neuropathological diagnosis.

Cerebral infarction. An infarct, which is the consequence of a focal or generalized disorder of cerebral
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circulation that occurs during the antenatal or early postnatal periods, is a relatively rare cause of brain damage. It is presumed to be the result of embolization arising from placental infarcts or of thrombosis caused by vascular maldevelopment, sepsis, or asphyxia.

In the series of Fujimoto and colleagues, 22% of cerebral infarctions followed perinatal asphyxia. About half of infants have an antecedent neonatal encephalopathy, and about a third have a thrombophilic abnormality, usually heterozygosity for factor V Leiden, or a high factor VIII concentration.

The anatomical consequence of cerebral infarction is usually a porencephalic cyst, which is an intraparenchymal cyst that communicates with the ventricular system and is partly and usually sparsely covered by ependyma. The clinical correlates are generally a spastic hemiparesis, hemisensory deficits, and often hemianopsia.

**Evolution of Motor Patterns in the Asphyxiated Infant**

Infants in whom perinatal asphyxia occurs experience various sequential changes of muscle tone and an abnormal evolution of postural reflexes. Most often, a gradual change from the generalized hypotonia in the newborn period to spasticity in later life is seen. The earliest sign of spasticity is the presence of increased resistance on passive supination of the forearm, or on flexion and extension of the ankle or knee.

In spastic diplegia, this abnormal stretch reflex is first evident in the lower extremities and is often accompanied by the appearance of extension and scissoring in vertical suspension, the late appearance or asymmetry of the placing response, a crossed adductor reflex that persists after 8 months of age, and the increased mobilization of extensor tone in the supporting reaction. In spastic hemiplegia, abnormalities first become apparent in the upper extremity.

When 5 infants with unilateral hemispheric lesions detected by routine imaging studies during the first week of life were subjected to regular neurological examinations, no abnormalities could be detected until 3 months of age, when 1 of the infants showed an asymmetrical passive extension at the popliteal angle. Between 3 and 6 months of age, the signs were subtle and usually consisted of asymmetrical kicking in vertical suspension, which was seen in 3 in- fants by 6 months of age. Hand preference became apparent between 3 and 9 months of age.

In some instances, asymmetries of generalized movements and "fidgety" movements can be detected as early as 3 weeks of age. The absence of "fidgety" movements are also a good predictor of the development of dyskinetic and spastic quadriparetic cerebral palsy.

As a rule, the more severe the hemiplegia, the earlier the abnormalities make their appearance. Other signs of hemiparesis include inequalities of muscle tone, asymmetry of fisting, and inequalities of the parachute reaction. In many instances, parents also note poor feeding and frequent regurgitation.

A stage of intermittent dystonia often becomes apparent when the infant is first able to hold up his or her head. At that time, abrupt changes in position, particularly extension of the head, elicit a response that is similar to extensor decerebrate rigidity. Probably, the frequency with which this intermediate dystonic stage is observed is a function of the care with which neurological observations are performed. In the majority of children, dystonic episodes are present from 2 to 12 months of age. Ultimately, as rigidity appears, episodes become less frequent and more difficult to elicit.

In a smaller number of children with cerebral palsy, a transition occurs from the diffuse hypotonia seen in the neonatal period to an extrapyramidal form of cerebral palsy. Although a characteristic feature of the motor activity of the healthy premature and full-term infant is the presence of choreo-a-thetoid movements of the hands and feet, the fully developed clinical picture of dyskinesia is not usually apparent until the second year of life. Until then, the neurological picture is marked by persistent hypotonia accompanied by retention of the immature postural reflexes. In particular, the tonic neck reflex, the righting response, and the Moro reflex are retained for longer periods in infants with extrapyramidal cerebral palsy than in those in whom a spastic picture predominates.

In general, the earliest specific evidence for extrapyramidal disease is observed in the posturing of the fingers when the infant reaches for an object. This can be noted as early as 9 months of age, and as a rule, the early appearance of extrapyramidal movements indicates that the ultimate disability will be mild. In the child with dyskinesia, dystonic posturing can be elicited by sudden changes in the position of the trunk or limbs, particularly by extension of the head.

Every physician examining infants suspected of having a cerebral birth injury has encountered a patient who appears to have clear-cut neurological signs in early infancy but whose motor dysfunction resolves on subsequent examinations. Many of these infants have not escaped brain damage, though. Follow-up studies show them to have delayed milestones and a high incidence of
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mental retardation. Still, approximately a third appear normal or may demonstrate only mild perceptual handicaps or hyperkinetic behavior patterns.41

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