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The problem of neonatal and infantile asphyxia is long standing. Whereas there were many clinical and pathology papers studying asphyxia before 1975, the most important scientific examination of the pathophysiology of hypoxia was initiated by Myers in that year (1). He described several patterns of perinatal brain damage and their occurrence in primates. In these experiments, the author induced prolonged partial asphyxia and total asphyxia in the term monkey fetuses. Each was induced by a variety of techniques that impaired placental gas exchange; eg, maternal hypotension, maternal hypoxemia, and umbilical cord compression. In total hypoxia, brain stem injury predominated. In monkeys subjected to severe partial hypoxia, plus relatively short episodes of total asphyxia, the animals sustained lesions of the basal ganglia and cortex.

Volpe, in his classic 1981 textbook *Neurology of the Newborn,* made clinical correlations between human neonates and term monkey fetuses (2). Volpe noted selective neuronal necrosis in neonatal hypoxia and ischemic encephalopathy in the following areas: the hippocampus, which is injured more than the cortex; the diencephalon, especially the thalamus, hypothalmus, and lateral geniculate body; the basal ganglia, especially the caudate nucleus, putamen, and globus pallidus; the midbrain, especially the inferior colliculus, oculomotor and trochlear nuclei, red nucleus, substantia nigra, and reticular formation; the pons, especially the motor nuclei of the trigeminal and facial nerves; the medulla, especially the dorsal motor nuclei of the vagus nerve and nucleus ambiguous; and the cerebellum, especially the Purkinje cells and dentate nucleus.

The pathologic abnormalities of human neonatal hypoxia-asphyxia had been documented for many years, and was represented well in 1975 by Schneider et al, who described subcortical lesions in seven neonates after transient and circulatory arrest and asphyxia (3). The basal ganglia, diencephalon, tegmentum, brain stem, and spinal gray matter exhibited extensive necrosis in a columnar pattern. Lesions of the telencephalon and cerebral cortex were less prominent.

Di Chiro et al reviewed the pathogenesis of periventricular leukomalacia, which was based on impaired cerebral perfusion with emphasis on border-zone areas of injury paralleling the lateral ventricles, typical of hypoperfusion in the fetal circulation. In 1978, a primitive electron magnetic image could reveal periventricular low attenuation on a CT scan, but there was no attempt to characterize the other pathologic results of hypoxia-ischemia (4).

The first large, methodical study of the correlation between CT and autopsy in premature and full-term neonates with perinatal asphyxia was reported by Flodmark in 1980 (5). He and his colleagues studied 90 neonates. Although they could detect bleeding readily, whether from the germinal matrix or other sources, they concluded that it was extremely difficult, if not impossible, to evaluate the hypodensity of hypoxia-ischemia against the backdrop of the healthy, hypodense brain.

With the advent of the newer CT scanners, Adsett, Fitz, and Hill reviewed 56 asphyxiated term infants and correlated the CT findings with short-term neurologic outcome (6). Their study, in which a higher resolution scanner was used, was able to record focal hypodensity in two or more areas, including the basal ganglia, in 28 patients. Fifteen of these patients had a subsequent major handicap and five died; only two patients were healthy. The term ''decreased density'' was defined to include ''two or more focal areas of decreased density, or decreased density of the basal ganglia,'' so that findings obtained from the infants were not labeled ''decreased density'' based on the condition of the basal ganglia alone.

McArdle and colleagues studied 85 infants with a 0.6-T MR imaging unit; 82 of them were 29–44 weeks old (7). They found that in premature neonates with very watery, low intensity white matter on T1-weighted images, sonography was better than both CT and MR in depicting parenchymal changes of infarction or edema. After 37 weeks of gestation, however, MR imaging was superior. Eighteen patients had histories of a hypoxic-ischemic insult. While MR imaging allowed for the recognition of infarcts, and their series defined delayed myelination, there was no detailed analysis of basal ganglia or cortical abnormalities associated with hypoxia.

At this time, Barkovich took up the challenge of diagnosis in the neonate and infant. In his article, *Normal Maturation of the Neonatal and Infant Brain,* he defined the normal appearance of the brain by using the l.5-T MR scanner (8). Eighty-two infants ranging in age from 4 days to 2 years, all thought to be healthy clinically, were included. This article documented the evolution of myelina-

tion and pointed out that myelination can be evaluated best in the first year of life on T1-weighted sequences; T2-weighted images appeared to offer better evaluation of the associated changes of water loss. Barkovich noted the finding of high signal intensity in the peritrigonal white matter on T2-weighted images as a normal finding. He found that the high signal areas, which lay posteriorly and superiorly to the trigones, were areas of known delayed myelination involving the association areas called ''terminal areas'' by Yakovlev (9). Periventricular leukomalacia could be distinguished because it was more sharply defined and located more anteriorly and inferiorly, near the optic radiations. Barkovich's article, describing the normal condition of the brain, laid the groundwork for the three investigations describing pathologic abnormalities that followed.

Brain Damage from Perinatal Asphyxia: Correlation of MR Findings with Gestational Age was written in 1990 (9). Twenty-five patients who suffered asphyxia at known gestational ages were reviewed. The pattern of brain damage shown on MR images in these patients who had prolonged partial asphyxia, appeared to correspond predictably to the known maturation of the brain and its vascular supply. Patients at 24–26 weeks of gestational age had irregularly enlarged trigones with minimal periventricular gliosis. Patients at 28–34 weeks had variably dilated ventricles with periventricular gliosis. A single 36-week-old neonate had mild cortical and subcortical atrophy, gliosis superimposed on deep white matter, and periventricular gliosis. Term neonates had significant cortical and subcortical gliosis and atrophy in the parasagittal watershed areas. Post-term neonates at 44–46 weeks showed adult-pattern cortical and subcortical watershed gliosis and atrophy, but with sparing of the immediate periventricular region, which one associates with hypoperfusion in the fetal circulation. Finally, two children who suffered complete circulatory arrest showed a different pattern, with damage in the thalami, basal ganglia, and midbrain. This case presaged Barkovich's 1992 classic, *MR and CT Evaluation of Profound Neonatal and Infantile Asphyxia* (10).

In this article, Barkovich addressed profound asphyxia (cardiocirculatory arrest, abruptio placenta), in full-term neonates, in contrast to his later study of profound asphyxia in premature infants, written in 1995 (11). The investigation described 16 patients who suffered profound ischemic injury in the perinatal period of 1 week to 4 weeks (12 patients) and postnatal injury at 12 months to 23 months (4 patients). In the perinatal injury group, MR images showed shortened T1 and T2 prolongation in the ventrolateral thalami, posterolateral lentiform nuclei, posterior mesencephalon, and hippocampi. Follow-up years after injury showed atrophy and T2 prolongation in these regions, and also in the lateral geniculate nuclei and perirolandic cerebral cortex. In the second group, in which asphyxia took place in infancy, subacute MR images showed T2 prolongation in the corpus striatum and in most of the cerebral cortex, but not in the perirolandic cortex. Follow-up MR images showed atrophy in the same areas, as well as in the lateral geniculate nuclei and hippocampi.

All of the changes depicted by MR imaging reflected precisely the location of injuries in patients with profound asphyxia as described in the pathology literature. Barkovich suggested that the difference between MR studies and the known disease was that MR examinations revealed considerably less brain stem injury; the patients with severe brain stem injuries presumably succumbed without an MR examination, and therefore were not seen in the study.

In addition to describing these findings in detail, Barkovich developed two compelling hypotheses. The first postulated that the appearance of acute brain degeneration after hypoxic-ischemic injury is identical to that following glutamate-induced damage at *N*-methyl *D*-aspartate (NMDA) binding sites, and that in cases of hypoxic-ischemic injury and excitotoxic damage (induced by amino acids, glutamate, aspartate, and related compounds), the effects can be blocked by the administration of NMDA antagonists. The second hypothesized that areas undergoing active myelination are highly susceptible to injury in profound hypoxic-ischemia in neonates. Many studies have shown that myelination in the neonate is present in the ventrolateral thalami, dorsal lentiform nuclei, lateral geniculate nuclei, cortical spinal tracts extended up to the perirolandic cortex (partially myelinated at birth), as well as the dorsal brain stem. As the process of myelination is energy-intensive, Barkovich proposed that the process of myelination, superimposed upon a transiently high local concentration of excitatory amino acid NMDA receptors in the neonate brain, make these regions susceptible to profound hypoxic damage.

In summary, Barkovich first familiarized himself and his readers with the normal appearance of the neonate and infant brain with high-quality MR images. He studied the physiologic and pathologic data available long before the advent of high-quality MR studies, and gathered data from later MR studies on hypoxic injuries at different times in fetal life. He initiated studies of the effect of profound hypoxia in the perinatal and postnatal periods, ultimately correlating the observed damage with physiologic and biochemical correlates of excitatory amino acids and developmental myelination. His conceptual thinking and attention to detail make this investigation one of the 10 best scientific articles in neuroradiology in the last century.

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