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Encephalopathy of Congenital Heart Disease– Destructive and Developmental Effects Intertwined

Remarkable improvements in cardiac surgical techniques for newborns and very young infants with complex congenital heart disease (CHD) have led to pronounced increases in survival; however, neurologic sequelae are still common and generally range from 25% to 50%.[1,2] In recent years, a large literature has begun to define the anatomic features of the brain disturbance with CHD, the underlying neurobiological mechanisms, and the relationship with later neurologic consequences. As discussed later, there appears to be a remarkable similarity between certain aspects of the brain disturbance in CHD and those recently delineated in more detail in preterm infants.

See related article, p 1121

Insight into the anatomic features of the brain disturbance in CHD has been provided by conventional neuropathological studies postmortem and by magnetic resonance imaging (MRI) analyses in vivo. Neuropathological studies indicate that the brain disturbance in CHD before surgery is dominated by cerebral white matter injury (WMI), generally comparable with periventricular leukomalacia (PVL) as described in preterm infants.[3-5] The incidence of such injury at postmortem examination ranges from 50% to 100%. Neuronal loss and gliosis in the cerebral cortex, thalamus, basal ganglia, and brainstem/cerebellum are less marked but relatively frequent (approximately 50%). Cerebral infarcts, multifocal parenchymal hemorrhage, and watershed injury are less common accompaniments.[3,4] These various destructive lesions are accentuated after cardiac surgery and cardiopulmonary bypass.[2,6,7] Overt disturbances in early brain development do occur but are unusual (10%),[8] whereas abnormalities referable to later developmental events (20-40 weeks gestation) are somewhat more common; impairments of gyral development were noted in 21% of one large series.[8] Thus, overall, conventional neuropathology principally shows a particular predominance of cerebral WMI, frequently with accompanying neuronal injury in multiple nuclear structures.

MRI studies of infants with complex CHD have confirmed the prominence of WMI, but notably also suggest an admixture of important disturbances in later brain development. Thus, depending somewhat on the severity and nature of the cardiac lesion and the timing of surgery, approximately 20%-50% exhibit MRI features of overt WMI.[6,7,9-11] (Because the focal necrotic lesions of PVL are usually microscopic in size, these conventional MRI assessments likely underestimate the full extent of WMI.) In addition to WMI, however, advanced MRI techniques, including diffusion tensor, volumetric, and spectroscopic methods, have provided findings consistent with cerebral white matter "immaturity."[12-15] Overall diffusion and anisotropic diffusion measures in newborns with CHD are similar to those seen in infants approximately 4 weeks less mature. Disturbances in anisotropic diffusion involve primarily radial diffusivity, consistent with a disturbance of premyelinating oligodendrocyte (pre-OL) ensheathment of axons in preparation for myelination, which occurs postterm in the human cerebrum.[16,17] The advanced MRI techniques also show that brain abnormalities in newborns with CHD involve cerebral cortical and deep nuclear structures, with well documented decreases in cortical surface area and cortical folding/gyral development.[18] Indeed, such abnormalities have been identified by fetal MRI.[19] In this issue of *The Journal*, Owen et al[20] describe impaired volumetric development of the thalamus and basal ganglia. In addition, fetal MRI studies have documented impaired brain volumetric development, with apparent onset at approximately 28 weeks gestation.[21] Chronic hypoxia-ischemia appears to be the primary initiating pathogenetic factor.[1] Thus, considered

CHD	Congenital heart disease
GABA	γ-Aminobutyric acid
MRI	Magnetic resonance imaging
pre-OL	Premyelinating oligodendrocyte
PVL	Periventricular leukomalacia
WMI	White matter injury

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together, the conventional neuropathological studies and the advanced MRI data suggest that the brain abnormality in infants with CHD is a complex mixture of destructive and developmental disturbances.

Insight into the neurobiological mechanisms likely operative in infants with CHD is provided by recent work with preterm infants demonstrating that the brain abnormality originates and evolves over a similar maturational period (the last trimester of gestation), is caused particularly by hypoxia-ischemia, is primarily chronic, and involves a complex amalgam of destructive and developmental disturbances, affecting particularly white matter but also multiple neuronal/axonal structures.[16] The details of this amalgam have been elucidated in greater detail in preterm infants and likely are highly relevant to infants with CHD as well. In preterm infants, advanced neuropathological studies point to abnormalities of specific cerebral white matter constituents (ie, pre-OLs, axons, subplate neurons, and late-migrating γ-aminobutyric acid [GABA]-ergic neurons), as well as cerebral cortex and deep nuclear structures, especially the thalamus.[16] Pre-OLs are by far the most dominant cells of oligodendroglial lineage in human preterm white matter, accounting for 90% of the lineage at 28 weeks gestation and 50% near term.[22] Not until the postterm period do mature myelin-producing oligodendrocytes start to gain prominence.

Pre-OLs are exquisitely vulnerable to hypoxia-ischemia and are injured by a cascade involving excitotoxicity, microglial activation, and generation of free radicals.[17] The pre-OL injury initially includes cell death or survival with loss of cell processes, followed by proliferation of progenitors and replenishment of the vulnerable pre-OL pool (with propensity to repeat hypoxic-ischemic injury) but, ultimately, failure of maturation of these pre-OLs after termination of the hypoxic-ischemic insults, with resulting impaired myelination.[17,23-25] Importantly, an essentially identical scenario has been shown recently in an experimental model of hypothermia, circulatory arrest, and cardiopulmonary bypass.[26] This scenario with replenishment but maturational failure of pre-OLs may explain the MRI findings of white matter immaturity in newborns with CHD.

Also of potential relevance to infants with CHD, advanced neuropathological studies of preterm infants with PVL have elucidated effects on other developing white matter components, including axons, subplate neurons, and late-migrating GABAergic neurons. Axons are in a state of very active development in the third trimester,[27] and in preterm infants with PVL, many axons undergo degeneration.[28] This degeneration could lead to impaired development of the cerebral cortex and thalamus by anterograde and retrograde mechanisms, consistent with recently reported MRI and neuropathological data in preterm infants.[16] Developing axons were shown to be particularly susceptible to hypoxic-ischemic injury in a neonatal rat model.[29]

Subplate neurons are a transient population of neurons beneath the cortical plate in the third trimester in the human brain[30]; these cells are critical as sites of transient synaptic contact for thalamocortical, corticocortical, and commissural cortical fibers that are rapidly developing during this period.[31,32] Subplate neurons also have been shown to be vulnerable to hypoxia-ischemia in a neonatal rat model.[33] Recent studies in preterm infants demonstrated diminished subplate neurons in association with PVL.[34] Based on experimental studies, the consequences of subplate neuron loss are impaired cortical and thalamic development, as detected by MRI in living preterm infants.[16]

Late-migrating GABAergic neurons, destined for superficial layers of the cerebral cortex and thalamus, also are abundant in cerebral white matter in the third trimester human brain.[35] Injury to these neurons results in impaired cerebral cortical development, along with such functional deficits as heightened excitability and disturbed specification of cognitive critical periods. A neuropathological study of preterm infants with PVL detected a loss of these migrating neurons.[36]

The advanced neuropathological studies that revealed these effects on white matter neuronal/axonal structures in preterm infants have not yet been applied to infants with CHD. Nevertheless, the MRI findings described earlier in infants with CHD suggest that these effects likely occur.

In addition to the aforementioned cerebral white matter neuronal/axonal components, cerebral cortical neurons, actively differentiating in the third trimester, are affected in preterm infants with WMI.[37] The MRI data raise the possibility of this effect in infants with CHD as well. The disturbance in development may be related either directly to hypoxia-ischemia or secondarily to axonal or subplate neuron disturbances. A recent study in an experimental model of chronic hypoxia and WMI clearly showed impaired cortical differentiation.[38] Finally, a detailed neuropathological study found affects on the thalamus in at least 60% of preterm infants with PVL.[39,40] Similarly, thalamic neuronal loss and gliosis were identified in approximately 50% of infants with CHD studied neuropathologically.[4] Whether these affects on the thalamus reflect primary hypoxic-ischemic injury (because of the high metabolism and concentration of excitatory amino acid receptors in thalamus) or secondary anterograde and retrograde effects related to white matter axonal and subplate neuron disturbance is unclear, but it is likely that at least one of these phenomena accounts for the decreased thalamic volume documented by MRI in living infants with CHD.[20]

Clearly, advanced neuropathological studies of the brain in infants with CHD are needed to determine conclusively whether these infants sustain the same changes in the white matter and nuclear structures described in preterm infants. Nevertheless, in view of the similarities in terms of timing and nature of insults, prominence of WMI, and MRI data showing cortical and thalamic underdevelopment, it seems likely that the brain abnormality in infants with CHD will prove to be a complex amalgam of destructive and developmental disturbances, as we have described in preterm infants.[16] Indeed, the term coined for the combination of white matter and neuronal/axonal abnormalities in premature infants, the "encephalopathy of prematurity,"[16] perhaps could be appropriately modified in this context to the "encephalopathy of CHD."