New Concepts in Perinatal Hypoxia Ischemia Encephalopathy

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This article summarizes recent insights into perinatal hypoxic-ischemic brain injury in the neonate. Before effective treatments can be offered, diagnosis, timing, and an understanding of the pathogenesis are imperative. The analysis of appropriate animal models is also summarized in this review. These models have provided interesting evidence that after hypoxia ischemia, progenitor cells in the postnatal brain are stimulated to generate new neurons and oligodendrocytes. The role of these newly generated cells is unclear, and mechanisms of migration and survival are currently being elucidated. A discussion of more recent imaging techniques, such as diffusion tensor imaging, is provided. This allows for improved understanding of the microstructural organization of white matter and how this is altered by hypoxic-ischemic injury. Neuroprotection with hypothermia is now occurring in full-term neonates that meet clinical criteria; however, specific therapies such as inhibition of non–*N*-methyl-D-aspartate receptors may offer improved outcomes by targeting specific pathways and populations of cells.

Introduction

Perinatal hypoxia ischemia (HI) is an important cause of neonatal brain injury and is associated with long-term neurologic sequelae such as cognitive dysfunction, developmental delay, seizures, and sensory or motor impairment [1–3]. Advancements in neonatal care, neuromonitoring, and the ability to offer neuroprotection with hypothermia in select full-term infants with encephalopathy now provide the opportunity for pediatric neurologists to play a crucial role in the neonatal intensive care unit.

This report reviews the diagnosis of hypoxic-ischemic encephalopathy (HIE) and presents recent advances in our understanding of the pathophysiology, neuroimaging, and therapeutic strategies for both the preterm and term neonates that have undergone HI brain injury.

Diagnosis

HI is one of the many causes of neonatal encephalopathy and is a major contributor to morbidity and mortality in infants and children [4]. HI of the newborn is defined as an event that results in decreased oxygen and blood supply to the brain. The diagnosis of HIE requires evidence for an event that results in both ischemia and hypoxia either before, during, or after birth. Careful review of the history, a thorough neurologic examination, and review of laboratory data are crucial in determining if HI is the cause of the encephalopathy. All aspects of the maternal history must be thoroughly reviewed, along with details of the pregnancy, labor, delivery, and postnatal events. Analysis of placental pathology is strongly recommended but often not performed. Low Apgar scores, respiratory failure, intrauterine asphyxia, postnatal cardiac insufficiency, uteroplacental insufficiency (eg, abruption or uterine rupture), and disturbances of labor or delivery (eg, decreased fetal movements, vaginal bleeding, and fetal heart irregularities) would help differentiate the heterogeneous causes of neonatal encephalopathy and HIE. The clinical features and extent of injury are dependent on the time of onset and severity and duration of the insult. The initial neurologic examination includes, but is not limited to, depressed level of consciousness, respiratory disturbance, constricted pupils, dysconjugate gaze, hypotonia, and seizures. Laboratory data, such as the cord and infant arterial pH and base deficit, may reflect the degree of injury.

It is important for the clinician to note that the preterm and term infant have different clinical and neuropathologic manifestations of HI. In premature infants, the clinical features of encephalopathy resulting from brain injury are difficult to recognize, and gestational age should be taken into consideration. The encephalopathic infant is a diagnostic challenge that requires thorough investigation. Antepartum events such as maternal thyroid disease, congenital anomalies, family history of seizures, and abnormal placenta, as well as intrapartum events, such as maternal fever and infection, are important etiologies of neonatal encephalopathy [5,6••]. A differential diagnosis must be

thoroughly investigated and clear evidence of an asphyxiated etiology should be apparent [7••,8••]. The importance of recognizing early clinical indicators of brain injury is imperative so that interventions may be commenced in a timely fashion [9,10].

Pathophysiology

The pathogenesis of hypoxic ischemic injury is complex. The severity of the insult, the gestational age, and the timing and duration of brain injury are important determinants of the resulting pathology that develops [4]. HI injury in the term infant commonly affects the gray matter (neuronal), whereas in the preterm infant the result is periventricular leukomalacia (PVL) or more diffuse periventricular white matter injury (PWMI) [1,2,11]. This selective vulnerability of certain brain regions and populations of cells is thought to be a result of maturational factors.

Deprivation of oxygen and glucose (two essential energy sources) to the brain causes neuronal injury and death. This effect is deleterious at a time when intense neuronal and glial development is occurring. The degree of injury is influenced by the severity and duration of the insult. The greater and more long-lasting the insult, the more neurons and glia undergo cell death. The process of delayed neural cell death can be significant in severe insults [11]. Other factors that are important in determining pathologic outcome are temperature and metabolic status. The cellular pathogenesis of neuronal injury in the term and preterm infant has been reviewed elsewhere [1,11,12•]. In the preterm infant, however, the primary neuropathologic substrate for neurologic disturbances involves injury to the white matter.

PVL or PWMI is a disturbance in cerebral myelination, suggestive of oligodendrocyte progenitors and immature oligodendrocytes being the cellular target of injury. It has been reported that the timing of appearance of oligodendrocyte progenitors in human white matter coincides with the period associated with high risk for PWMI [13,14]. Back et al. [14], using human brain tissue from the parietal white matter at the level of the trigone of the lateral ventricles from autopsied brains, characterized the cellular events that occur with human immature oligodendrocytes. This study concluded that human myelinogenesis is characterized by three progressive phases that begin at approximately 30 weeks of gestation with a pre-myelin sheath (immature oligodendrocytes that wrap around the axon), which then progress to an immature sheath (initial phases of expression of myelin basic protein and other myelin proteins), and then the final myelin sheath (myelin basic protein is fully expressed and myelin is more mature) [14]. The importance of understanding which stages of oligodendrocyte development are susceptible to injury will give us a better understanding of the pathophysiology of PWMI. PWMI or PVL is a leading cause of brain injury in premature infants and the underlying cause of cognitive impairment and deficits in myelin volume as determined by brain imaging [4,15,16•].

Oligodendrocytes have diverse functional roles in the developing brain. They not only participate in myelination and axonal conduction, but also help maintain axonal integrity and directly participate in signaling networks with neurons via glutamatergic release and signaling [17••,18••]. The functional role and consequences of neuron-glial signaling in development are still being investigated and may have profound impact on cortical and deep nuclear neuronal development. MRI has shown that preterm infants with evidence of white matter injury had significant reduction of gray matter volumes at term and beyond [19,20,21•]. Interestingly, Kesler et al. [20] conducted a volumetric analysis of preterm infants at a mean age of 9.2 years and found that gray matter volumes were particularly reduced in the temporal lobes compared with controls; however, the gray matter volume in the frontal and parietal lobes was increased. Understanding normal brain development and the cellular processes that occur subsequent to injury such as HI will allow us to develop specific and targeted therapies.

Animal Models of HI

The study of HI brain injury has been in large part based on extensive research in animals. The main goals of the use of animal models are to increase our knowledge of the underlying mechanisms and evolution of injury, as well as providing opportunities to test therapeutic strategies. In order for the animal model to be relevant, it is necessary that it reflects the histopathologic spectrum of a specific injury to the developing brain, correlates with developmental changes observed in humans, and displays the functional outcomes seen in human pathology. A brief overview of some of the commonly used animal models of HI injury to the newborn brain is presented in the following text. More detailed information can be found elsewhere [22–24].

Small rodents are the most frequently used animals to study HI injury because they are readily available [22]. Currently, the main advantage of a rat or mouse model is that they have been well studied and characterized. Furthermore, a greater understanding of mouse genetics has allowed scientists to create transgenic mice that have altered expression of specific proteins. A review that extensively examines different variables of brain maturation found that a 7- to 14-day-old rat is most comparable with the term human brain [25]. A widely used model that has been useful in elucidating the short- and long-term effects of perinatal HI injury is the Rice-Vannucci model in rodents, where a unilateral permanent carotid artery ligation is made, which is followed by systemic hypoxia [26]. The duration of the hypoxia varies between different strains and/or species. Adaptations of this model in younger rodent pups have also been used in order to correlate developmentally with injury that occurs in the preterm infant.

Another model of interest is chronic sublethal hypoxia, where rodent pups are raised in sublethal hypoxia for 8 to 30 days [27,28•,29]. The resulting injury is representative of very low birth weight preterm infants, and ventriculomegaly, decreased white matter and gray matter volume, and long-term neurobehavioral changes are observed [27,28•,29].

Studying white matter injury commonly associated with the preterm infant has posed a challenge because of the difficulty in obtaining human tissue. However, it has been difficult to define the pathogenetic mechanisms underlying PWMI in the developing cerebral white matter using animal models. The immature sheep fetus may be a useful model to study PWMI because, in many respects, it is similar in development to a 24- to 28-week-old human fetus [30•]. Also, the size of the sheep allows the study of other aspects of injury, such as cerebral blood flow and electroencephalographic recordings. However, one limitation of using the sheep as a model is the inability to rapidly manipulate or alter its gene expression.

Advances in our understanding of mouse genetics and of the molecular mechanisms that regulate gene expression have allowed scientists to develop transgenic or null-mutant mouse strains. The use of these mice will allow us to study how molecular manipulation of key regulatory genes affects HI injury. These mice also provide the opportunity to analyze the identity and lineage potential of postnatal neural cell populations that are expanded as a result of injury. Finally, the ability to target specific cell lineages will allow us to gain a better understanding of how specific aspects of brain development are affected or altered after HI injury. This will also provide us with a better understanding of the cellular and neurobiologic substrates involved in perinatal injury.

The development of animal models for perinatal HI injury will facilitate translational research. There are both strengths and limitations to these models. The developing brain is complex and one must recognize that there are (mouse) strain differences in the susceptibility to HI injury [31]. It is also important that correlations are made with long-term neurobehavioral and neuropathologic outcome data. Roohey et al. [22] did an extensive review of the literature on neonatal HI animal models and found that only a small percentage (29%) of studies tested outcome more than 24 hours after injury. It is imperative that the proper model, strain, and number of animals necessary to compensate for within-strain variability be chosen depending on what aspect one wishes to study.

Neurogenesis and Gliogenesis After HI

An interesting finding from animal models of HI brain injury is that the postnatal brain contains an endogenous pool of multipotent progenitor cells with the capability of proliferating and differentiating to produce new neurons and glia after injury [32,33]. The germinative zones where these cells are located are at the subventricular zone (SVZ) adjacent to the lateral ventricles and the dentate gyrus. The SVZ is of particular interest because in humans it is prominent in the third trimester and is referred to as the germinal matrix. This region is comprised of immature cell types that are at different stages of lineage restriction [34]. Evidence in animal models suggests that postnatal brain injury such as HI activates this region, increasing the proliferation rate and the number of progenitor cells [34,35]. The number of SVZ progenitor cells is larger in the newborn brain as compared with the adult [36], leading one to speculate that the immature brain may have a greater capacity to recover from injury than the adult brain (often referred to as the Kennard principle).

The identification of these progenitor cells in the SVZ and the mature cell types they generate has been in large part due to the increased availability of biomarkers. Table 1 lists some of the commonly used immunohistochemistry markers. Other methods include retroviral labeling and injections of a synthetic nucleoside, 5-bromo-2-deoxyuridine, which is an analogue of thymidine that is incorporated into newly synthesized DNA during the S phase of the cell cycle. The fate of these precursors is heavily influenced by their final anatomic destination (ie, the brain regions where they migrate and differentiate). In models such as the Levine-Vannucci model of HI in rodent pups, experimental evidence indicates that neuronal progenitor cells from the SVZ generate new neurons and oligodendrocytes [36–38]. This robust proliferative response continues for up to 1 to 3 weeks after HI injury [39], and many of the newly generated neurons migrate to the site of injury [40]. However, only limited data exist on whether this expansion and proliferation of SVZ progenitors can compensate for the loss of oligodendrocytes and neurons, and whether this response is sustained months after injury.

A recent study demonstrated a robust production of new neocortical neurons after HI [41]. Using injections of 5-bromo-2-deoxyuridine, the authors found a significant increase in the number of doublecortin-positive–expressing cells, with morphologies of migrating neuroblasts interspersed between the ipsilateral SVZ and neocortex at 2 and 5 weeks after injury. These neurons exhibited the capacity to fully differentiate within 5 weeks after injury. This study was unique in that it demonstrated continued generation of doublecortin-positive– and neuronal nuclei–positive cells in the ipsilateral neocortex at 5 months after injury. However, consistent with data from other laboratories [40,42,43], a significant number of newly generated neurons degenerated and their overall rate of survival was low. It is not clear why all the newly formed progenitor cells cannot be sustained, but it is suggested that this is due to lack of proper trophic factors [41,42].

The route by which the newly generated cells migrate to the injury is unclear. Many studies documented an SVZ origin; however, the pathway by which these cells repopulate the injured site is not known. Using retroviral

Table 1. Identification of different postnatal brain cells using immunocytochemistry

Class	Antibody marker	Abbreviation	Lineage	Location
Mitotic cells	5-bromo-2-deoxyuridine	Anti-BrdU	Cells that are undergoing S phase and have incorporated BrdU into their DNA	Nuclear
		Ki-67	Cell proliferation	Nuclear
Precursor cells (neuron or oligodendrocyte)	Glial fibrillary acidic protein	GFAP	Astrocyte lineage	Intermediate filament protein
	Brain-derived lipid binding protein	BLBP	Radial-glia astrocyte lineage	Cytoplasm
	Nestin		Radial-glia astrocyte lineage	Intermediate filament
	Doublecortin	DCX	Migrating immature neurons	Cytoskeletal microtubule binding protein
	Chondroitin sulfate proteoglycan	NG2	Oligodendrocyte precursor cells	Cell surface
		DLX-2	Progenitors for inhibitory interneurons	Nuclear
		Mash1	Oligodendrocyte progenitors	Nuclear
	Polysialylated neural cell adhesion molecule	PSA-NCAM	Immature neurons	
Neurons	Neuronal nuclei	NeuN	Mature neurons	Nuclear
	Hu family	Hu	Immature neurons	Cytoplasm
Immature oligodendrocytes	Oligodendrocyte transcription factor 2	Olig 2	Oligodendrocyte lineage development; required for development of $NG2^+$ cells	Nuclear
Mature oligodendrocytes		Rip	Oligodendrocytes and their myelin sheaths	Cytoplasm
	Oligodendrocyte transcription 1	Olig 1	Oligodendrocyte maturation	Cytoplasm
		CC1	Mature oligodendrocytes	Oligodendrocyte cell bodies
	Myelin basic protein	MBP	Mature oligodendrocytes	Myelin membrane
	Myelin oligodendrocyte glycoprotein	MOG	Mature oligodendrocytes	Cytoplasm and peripheral processes

markers to label newly generated cells from the SVZ revealed that there is a stream of cells migrating from the SVZ to the olfactory bulb and to the white matter [29,40,42–44]. This stream is similar to the rostral migratory stream, which gives rise to new neurons in the postnatal olfactory bulb of rodents. These findings suggest that the new neurons generated after HI insult might migrate via this pathway. Independent studies showed that there are radial glia-like cells extending from the SVZ into the damaged striatum after injury that provide a cellular substrate supporting migration of newly formed cells into the damaged area [40,44]. However, factors that promote cell migration, such as chemokines, extracellular matrix components, or trophic factors, also play an important role in inducing migration and maturation of these cells at the injured site.

Key determinants in survival and expansion of the progenitor cells are neural growth factors. It has been shown that infusing the SVZ with growth factors promotes enhancement and recruitment of these cells. The intraventricular administration of fibroblast growth factor-2 and/or epidermal growth factor (EGF) was shown to increase the proliferation of cells in the SVZ and promote olfactory bulb neurogenesis and neuronal maturation [45,46]. Other factors such as platelet-derived growth factor and basic fibroblast growth factor are involved in pre-oligodendrocyte proliferation and migration, but their combined effects may prevent differentiation into mature oligodendrocytes

[47]. Activation of the EGF promotes oligodendrocyte process formation and regrowth after injury. Promising results demonstrated that, after a demyelinating lesion in adult mice, increased EGF receptor signaling enhanced oligodendrocyte regeneration and myelin repair [48•]. Whether enhancement of EGF receptor signaling will promote pre-oligodendrocyte expansion and recovery after PWMI remains to be elucidated.

Multipotent neural progenitor cells offer new insight into potential plasticity of the postnatal brain after injury and developmental neurobiology. Understanding their development, migration, and incorporation into an existing neural network surrounding injury is imperative because of their potential for repair and regenerative medicine. However, it is not known whether these new cells become fully functional or integrated into the surrounding neural circuitry. Future electrophysiologic studies, combined with functional imaging analysis, will define to what extent this occurs.

Neuroimaging

Significant advances in brain imaging have allowed clinicians to assess the extent of perinatal brain injury. Compared with head ultrasound and CT imaging, MRI allows for more detailed visualization of the HI insult [49••]. The use of MRI can help determine the timing and possibly the cause of injury. Follow-up studies can establish the relationship between the degree of injury and neurodevelopmental outcomes in the preterm and term infant [50–52,53•]. However, the use of conventional MRI is limited, especially in the newborn brain, which is not fully developed or myelinated. Diffusion-weighted imaging is often used and is helpful in identifying ischemic tissue, although studies in the neonate that have undergone HIE are limited and conflicting data have been reported [54]. Newer quantitative techniques are also being utilized, such as diffusion tensor imaging (DTI) and tractography. These studies will provide clinicians with additional information to help detect changes soon after injury and distinguish the degree of injury.

DTI and tractography

MRI has provided evidence that perinatal HI involves the cortical, subcortical, and specific white matter regions. Animal models of perinatal asphyxia have also shown that there is reduction of white matter volume. The association of brain injury with cognitive/behavioral deficits is not completely understood, especially pertaining to white matter involvement. Understanding how the degree of white matter injury correlates with neurodevelopmental outcomes is an undertaking best suited for DTI. DTI allows for better visualization of the white matter by providing quantitative measurements of water diffusion in brain tissue, reflecting density and spatial organization. In the white matter, the diffusion of water is directional and restricted along the lines of the axis of the myelin sheath bundle. This is referred to as anisotropy. The fractional anisotropy (FA) is a parameter calculated from the DTI data and represents the degree of anisotropy of water diffusion. FA values begin at zero (complete isotropic diffusion) and can approach one as the degree of diffusion decreases [55•].

The normal neonatal brain has undeveloped myelin. During early development, as myelination increases and the myelin bundles become more tightly packaged, the degree of anisotropy increases, thus increasing the FA. Brain injury may result in decreased FA, representative of loss of structural integrity. DTI allows us to visualize these pathways and provides us with a greater understanding of the microstructural organization of the white matter and the integrity and coherence of the bundled fibers. A study on DTI in full-term infants using FA found that this parameter is reduced in both moderate and severe brain injury, and that this may reflect a breakdown of white matter organization in the basal ganglia thalamic region and the posterior limb of the internal capsule [54]. The surprising finding of this study was that the FA and apparent diffusion coefficient (ADC) were abnormal with visible abnormalities seen on MRI. However, in a small group of infants, inspection of the white matter did not show abnormalities, the ADC was close to control values in the same region, and the FA was significantly reduced in the posterior and centrum semiovale white matter [54]. In a study by Rutherford et al. [56], ADC values were found to be significantly reduced in infants with severe HIE as compared with controls, although ADC values were normal or mildly increased in neonates with moderate HIE. Of note, the ADC values in the severe HIE group were almost normal after the first week of life, making it difficult to interpret ADC values or DWI without relation to timing of injury.

A longitudinal study of MRI, DTI, and ADC of premature infants, with and without white matter injury evident on MRI, found that anisotropy increased with age in all premature infants without white matter injury; however, those with mild injury had decreased anisotropy in the frontal white matter, whereas those with severe injury had decreased anisotropy throughout [57]. In the preterm infants with moderate white matter injury, the ADC failed to decrease and the anisotropy failed to increase in widespread regions of the brain that were normal on conventional MRI.

A limitation of DTI has been a lack of normative studies for comparison. Bartha et al [58••] addressed this by prospectively studying a cohort of healthy term neonates as a control group. This study established a database that could be used as a reference for those neonates that are being evaluated for brain injury. Data obtained from DTI has helped diagnose perinatal white matter injury [57,59]. DTI may also serve as a tool to improve detection of brain injury with HIE and, as studies are being performed, help in correlating neurodevelopmental outcome.

In a small study by Nagy et al. [60], DTI was performed on nine adolescents with no overt physical signs of cerebral palsy who on retrospective chart review had a history of being full term with at least a moderate degree of HIE. This selected population had, compared with controls, significantly lower FA values in several distinct brain regions, including the posterior limbs of the internal capsule and posterior corpus callosum [60]. Results from this study showed that adolescents with a history of moderate HIE have disturbances noted in specific white matter regions. Interestingly, eight of the nine adolescents had cognitive problems associated with attention and memory, and two thirds scored 85 or below on the Wechsler Intelligence Scale for Children IQ test.

Fiber tracking and directionally encoded color maps complement the information provided by DTI and may be feasible in neonates [61]. With fiber tracking, the information from DTI is reconstructed to produce a virtual three-dimensional representation. Directionally encoded color maps allow us to visualize with color schemes the dominant direction of the anisotropy, the direction of the fiber tracts, and the degree of anisotropy represented by brightness of color. Thus, directionally encoded color maps provide a simple and effective way to visualize the direction and orientation of the white matter tracts [62].

Measurements of FA were significantly decreased in patients with moderate and severe white matter pathology visualized on MRI in a recent study investigating both ADC values and DTI of full-term newborns who met strict criteria for HIE [54]. The decreased values of FA were more pronounced in the posterior white matter. Compared with their previous studies of ADC values, which tended to return close to normal after the first week of imaging, this group found that FA was statistically decreased even if the MRI was obtained later [54]. In addition, the anisotropy was significantly decreased in the basal ganglia and thalamic region in the first week and became progressively more abnormal in the ventrolateral nuclei. This study reinforces the fact that FA and DTI are sensitive indicators of injury.

Treatment

Currently, treatment of infants who have been diagnosed with HIE is supportive care with prompt recognition and treatment of seizures. Evidence from several adult and newborn animal studies indicates that reduction of brain temperature by 2°C to 5°C provides neuroprotection by preserving energy metabolism, reducing edema, and improving behavioral outcome. Based on animal studies, the window of opportunity in which therapeutic intervention is possible is estimated to be between 2 and 6 hours. The concept of hypothermia as a therapeutic approach is not a novel one, as Westin published a series of studies in the 1950s and 1960s showing that hypothermia was beneficial in perinatal asphyxia [63]. Recently, hypothermia has regained attention and is being offered to those infants who meet clinical and physiologic criteria. The two methods by which hypothermia is being conducted is with either head cooling or whole body hypothermia. Two large randomized trials have been recently conducted on hypothermia, and these studies included follow-up data on outcomes of these patients.

The first completed multicenter clinical trial used the Cool-Cap (Natus Medical, San Carlos, CA) method [64••]. Infants that met criteria consistent with moderate to severe encephalopathy due to HI received either selective head cooling with mild systemic hypothermia for 72 hours or supportive therapy. This study found that in the most severe cases, there was no evidence of benefit with the Cool-Cap; however, those infants in the less severe instances had significantly reduced combined mortality and major disabilities [64••].

The second large randomized controlled study was by Shankaran et al. [65••], who used whole-body hypothermia in cases that met criteria for moderate to severe encephalopathy. Cooling blankets maintained an esophageal temperature of 33.5°C ± 0.5°C for 72 hours. The control group received standard supportive care. The infants were reassessed at approximately 18 months of age and it was found that 45 of 102 (44%) in the hypothermia group had death or moderate/severe disability compared with 64 of 103 infants (62%) in the control group [65••]. This study found that the rate of disabling cerebral palsy was 19% in the hypothermia group compared with 30% in the controls.

Another promising therapy is the blockade of the AMPA–kainate-type glutamate receptor in order to decrease glutamate receptor–mediated excitotoxicity. Inhibition of non–*N*-methyl-D-aspartate receptors may not only prevent neuronal injury, but also immature oligodendroglial injury. Developing oligodendrocytes express ionotropic kainate and AMPA glutamatergic receptors [66]. In a study in both rodents and human brain tissue, it was demonstrated that there is a direct correlation between selective vulnerability to HI and expression of AMPA receptors lacking GluR2 [67,68]. This suggests that $Ca2^{+}$-permeable AMPA receptor blockage may represent an age-specific therapeutic strategy for use in humans. In a study on rodents, topiramate administered in vivo after HI insult was protective against white matter injury and decreased sensorimotor deficits [69]. Interestingly, protective doses of topiramate did not affect normal development and maturation of oligodendrocytes [69].

Many other potentially valuable interventions in preventing or ameliorating hypoxic ischemic injury are being studied. The reader is referred to Perlman [70••] and Volpe [1] for a more exhaustive review of the pathophysiology and possibilities of treatment. Potentially promising agents are ones that affect common pathways initiating injury and related downstream pathways. However, safety and use in clinical practice have been limited, and continued basic and clinical research will determine long-term benefits.

Conclusions

Advances in our understanding of the neurobiologic substrates of brain development are necessary in order to determine how injury alters this process. We are now gaining a greater understanding of the cellular substrates that are affected by brain injury such as HI. However, available imaging techniques in humans are currently not at a sufficient resolution to confirm what has been shown in animal models. Meanwhile, high-resolution imaging of small animals is rapidly developing, allowing scientists to study specific animal models of injury, including white matter damage. This will provide a link to the development and testing of new therapeutic strategies for neonatal brain injury. The clinician, now more than ever, possesses tools that are available to diagnose and visualize the injury, but it is still necessary to develop multimodality strategies that will promote recovery and improve outcomes.

Disclosures

No potential conflicts of interest relevant to this article were reported.

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