Hypoxic-Ischemic Encephalopathy in Neonates: Current Concepts in Diagnosis and Management

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Abstract

Hypoxic-ischemic encephalopathy (HIE) in neonates remains a significant cause of neurological morbidity and mortality globally, with substantial long-term consequences. It results from a period of impaired cerebral blood flow and oxygen delivery, typically occurring during labor, delivery, or the immediate postnatal period. The pathophysiology of HIE is multifactorial, involving an initial hypoxic insult followed by a cascade of secondary energy failure, excitotoxicity, inflammation, and apoptosis. Early identification of neonates at risk for HIE is crucial for initiating timely and effective interventions. Diagnosis of HIE is primarily clinical but is increasingly supported by neuroimaging techniques such as magnetic resonance imaging (MRI), which offers detailed insights into the extent and location of brain injury. Electroencephalography (EEG), especially amplitude-integrated EEG (aEEG), is a valuable tool for assessing severity and predicting neurodevelopmental outcomes. Biomarkers including serum S100B and neuron-specific enolase are under investigation for their potential role in early diagnosis and prognosis. Therapeutic hypothermia has emerged as the standard of care for moderate to severe HIE when administered within six hours of birth, significantly improving survival and reducing neurodevelopmental disability. However, its limitations, including partial efficacy and variable outcomes, have prompted exploration of adjunctive therapies such as erythropoietin, xenon gas, stem cell therapy, and anti-inflammatory agents. Current research also emphasizes individualized approaches based on severity, gestational age, and timing of intervention. This review aims to present updated insights into the diagnosis and management of neonatal HIE, highlighting recent advancements and emerging therapies. By synthesizing current evidence, it seeks to enhance clinical decision-making and improve neonatal outcomes. Continued research and multidisciplinary collaboration are essential for refining diagnostic strategies and optimizing therapeutic interventions in this vulnerable population.
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Keywords: *Hypoxic-Ischemic Encephalopathy, Neonates, Management*

Introduction

Hypoxic-ischemic encephalopathy (HIE) is a critical neonatal condition that arises from a lack of oxygen (hypoxia) and impaired blood flow (ischemia) to the infant's brain during the perinatal period. It remains a leading cause of neonatal mortality and long-term neurodevelopmental impairment worldwide, particularly in low- and middle-income countries. The global incidence of HIE is estimated to range between 1 and 8 per 1,000 live births, with higher rates in regions

lacking advanced perinatal care [1]. Despite improvements in obstetric and neonatal care, HIE continues to present significant clinical and ethical challenges, especially in cases where long-term outcomes are uncertain [2].

The pathophysiological basis of HIE is typically biphasic. The initial hypoxic insult disrupts cerebral metabolism, leading to decreased ATP production, ionic imbalance, and cell swelling. If reperfusion occurs, a secondary energy failure ensues within 6 to 48 hours, driven by excitotoxic neurotransmitter release, oxidative stress, mitochondrial dysfunction, and inflammatory responses [3]. This complex cascade of cellular events contributes to progressive neuronal injury and determines the severity of neurological outcomes. The degree and duration of hypoxia-ischemia, along with the infant's gestational maturity and ability to mount reparative responses, influence the clinical manifestation and prognosis [4].

Clinically, HIE presents with a range of neurologic signs, including altered consciousness, hypotonia or hypertonia, seizures, and poor feeding, often appearing within the first few hours after birth. The Sarnat staging system is commonly used to categorize the severity of encephalopathy into mild, moderate, and severe grades based on neurologic examination findings [5]. This classification aids in guiding early management decisions, particularly the initiation of neuroprotective therapies such as therapeutic hypothermia. However, the clinical presentation can be subtle or overlap with other neonatal conditions, necessitating careful evaluation [6].

The importance of early recognition and timely intervention in HIE cannot be overstated. Intervening during the latent phase—before the onset of secondary energy failure—offers the best opportunity to reduce irreversible brain injury. Therefore, strategies to enhance early diagnosis, including the use of advanced neuroimaging, EEG monitoring, and potential biochemical markers, are under continuous investigation. Moreover, management protocols continue to evolve with the integration of adjunctive therapies and personalized treatment approaches, aiming to improve both short-term and long-term outcomes [7].

The aim of this article is to provide a comprehensive overview of the current understanding of hypoxic-ischemic encephalopathy (HIE) in neonates, with a focus on recent advancements in diagnostic techniques and evolving management strategies. By synthesizing evidence-based knowledge, this review seeks to guide healthcare professionals in early recognition, risk stratification, and application of therapeutic interventions to improve clinical outcomes and reduce long-term neurological sequelae in affected neonates.

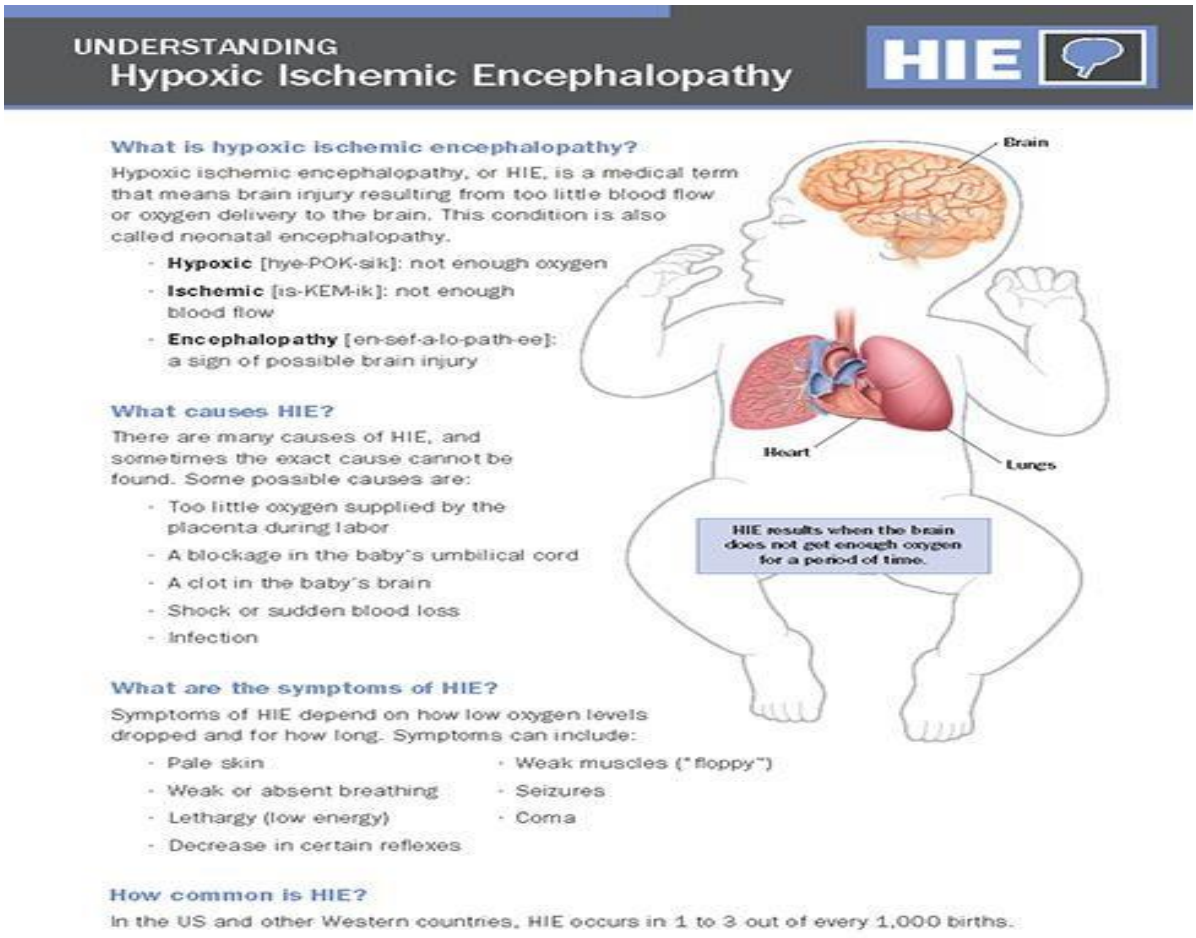

Figure 1: Understanding HIE [7].

Causes of Hypoxic-Ischemic Encephalopathy in Neonates

1. Antenatal Factors

Antenatal factors contributing to HIE are conditions that compromise oxygen delivery to the fetus during pregnancy. Maternal health issues such as preeclampsia, gestational diabetes, and infections like cytomegalovirus or toxoplasmosis can impair placental function, leading to reduced oxygen and nutrient supply to the developing fetus. Additionally, maternal substance abuse and severe anemia can exacerbate fetal hypoxia. Fetal conditions, including congenital heart defects and intrauterine growth restriction, also increase the risk of HIE by limiting the fetus's ability to tolerate hypoxic stress [1].

2. Intrapartum Factors

The intrapartum period, encompassing labor and delivery, presents several risks for HIE. Complications such as umbilical cord prolapse, placental abruption, uterine rupture, and prolonged labor can lead to acute interruptions in oxygen supply to the fetus. Abnormal fetal presentations, like breech position, and excessive bleeding during delivery further heighten the risk. These events can cause significant hypoxia and ischemia, resulting in neuronal injury if not promptly addressed [2].

3. Postnatal Factors

Postnatal causes of HIE involve conditions that impair oxygenation after birth. Respiratory failure, cardiac arrest, severe infections like sepsis, and persistent pulmonary hypertension can lead to inadequate oxygen delivery to the brain. Premature infants are particularly vulnerable due to underdeveloped lungs and immature cardiovascular systems. Additionally, traumatic birth injuries affecting the brain or skull can precipitate hypoxic-ischemic events in the neonatal period [3].

4. Placental and Umbilical Cord Abnormalities

Abnormalities in the placenta and umbilical cord can significantly impact fetal oxygenation. Conditions such as placental insufficiency, where the placenta cannot deliver adequate oxygen and nutrients, and umbilical cord compression or knots can lead to chronic or acute hypoxic events. These issues may go undetected until labor or delivery, emphasizing the importance of vigilant prenatal monitoring to identify potential risks for HIE [4].

5. Multifactorial and Idiopathic Causes

In some cases, HIE results from a combination of factors or remains idiopathic despite thorough investigation. The interplay between maternal, fetal, and environmental conditions can create a cumulative effect leading to hypoxic-ischemic injury. Factors such as low birth weight, low Apgar scores, and amniotic fluid contamination have been associated with increased HIE risk. Understanding these multifactorial causes is crucial for developing comprehensive prevention and management strategies [5].

Pathophysiology of Hypoxic-Ischemic Encephalopathy

Hypoxic-ischemic encephalopathy arises from a complex cascade of events following an episode of impaired cerebral oxygenation and perfusion. The initial phase of insult, known as the primary energy failure, occurs due to deprivation of oxygen and glucose, resulting in impaired mitochondrial oxidative phosphorylation and reduced adenosine triphosphate (ATP) synthesis. This leads to cellular depolarization, lactic acidosis, cytotoxic edema, and an influx of calcium and sodium ions, which contribute to neuronal dysfunction and necrosis [8]. Importantly, the severity and duration of this initial insult dictate the potential for reversible versus irreversible injury [9].

Following a transient period of partial recovery known as the latent phase, a secondary energy failure phase typically ensues within 6 to 48 hours post-insult. This phase is characterized by increased excitotoxicity, oxidative stress, mitochondrial permeability, and apoptosis. Glutamate, the primary excitatory neurotransmitter, plays a central role in initiating excitotoxic cascades by overstimulating NMDA and AMPA receptors, leading to intracellular calcium overload and activation of destructive enzymes like calpains and caspases [10]. Simultaneously, the generation of reactive oxygen species (ROS) exacerbates oxidative damage to DNA, proteins, and lipids, compounding the extent of neuronal injury [11].

The inflammatory response also contributes significantly to the pathogenesis of HIE. Microglial activation and the release of pro-inflammatory cytokines such as interleukin-1β and tumor necrosis factor-alpha amplify neuronal death and compromise the blood-brain barrier integrity [12]. Furthermore, mitochondrial dysfunction and impaired autophagy mechanisms limit the cell's ability to clear damaged organelles, perpetuating injury. These events create a vicious cycle of neuroinflammation and apoptosis, culminating in both focal and diffuse brain injury patterns

commonly seen in neonatal HIE [13].

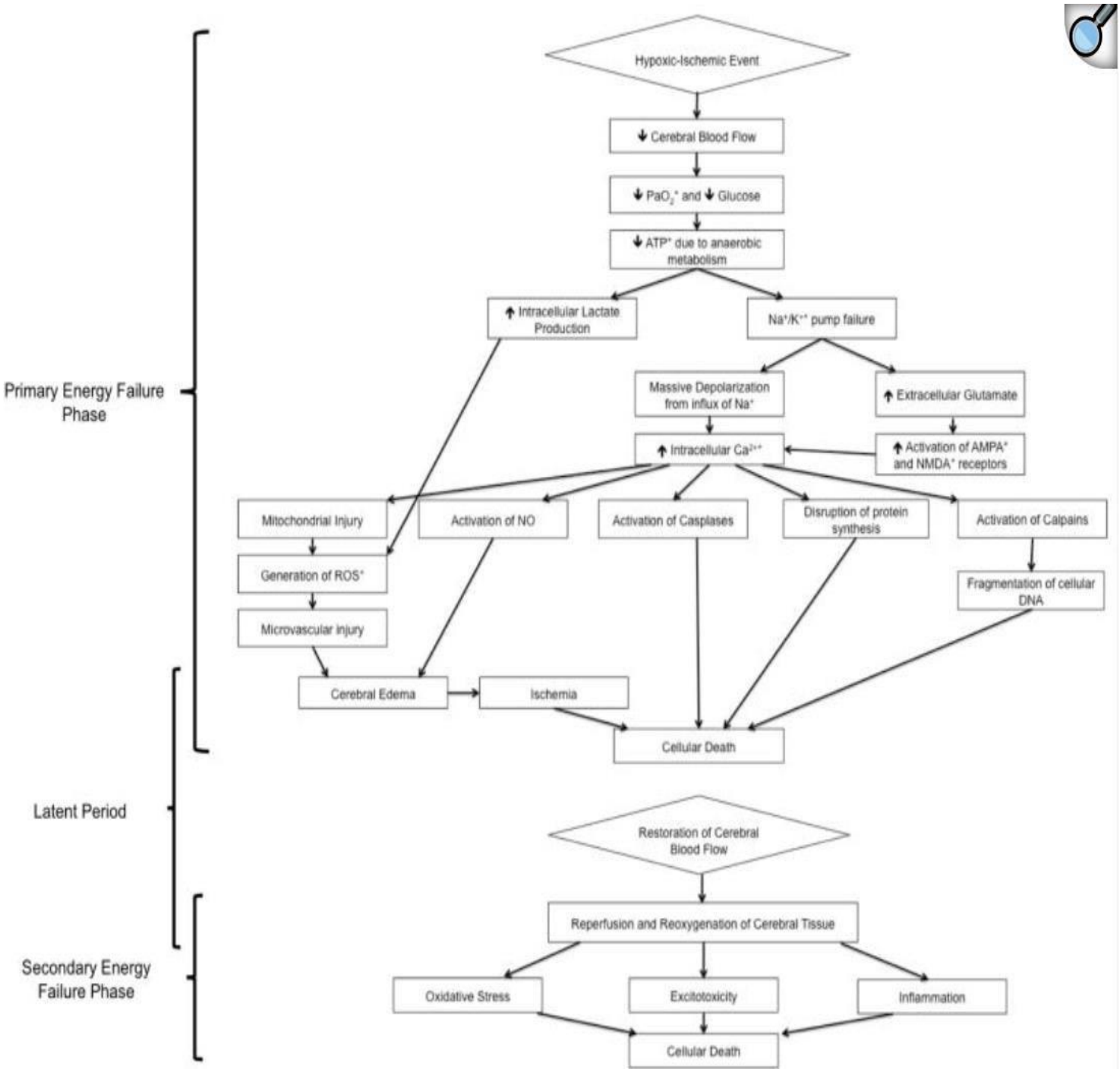

Figure 2: The Evolution of Hypoxic Ischemic Encephalopathy [6].

* Inline graphic = increased; Inline graphic = decreased; PaO2 = arterial oxygen; Na+ = sodium; K+ = potassium; ATP = adenosine triphosphate; Ca2+ = calcium; NMDA = N-methyl-D-aspartate; AMPA = ∝-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid; ROS = reactive oxygen species; NO = nitric oxide; DNA = deoxyribonucleic acid

Another important aspect of HIE pathophysiology is the difference in susceptibility based on gestational age. Preterm neonates are particularly vulnerable due to the immaturity of cerebral vasculature, limited antioxidant reserves, and underdeveloped autoregulatory mechanisms. In term infants, the pattern of injury often involves the basal ganglia, thalamus, and corticospinal

tracts, whereas preterm infants more frequently exhibit periventricular leukomalacia due to the

vulnerability of oligodendrocyte progenitors [14]. Understanding these developmental differences is essential for tailored therapeutic interventions and prognostication.

Animal models have been instrumental in elucidating the mechanistic pathways of HIE, particularly rodent and sheep models that replicate the biphasic injury pattern seen in humans. These models have facilitated the testing of neuroprotective agents, deepening our understanding of the cellular and molecular underpinnings of the disease. Ongoing translational research continues to explore novel targets to mitigate secondary brain injury and promote regeneration, with an emphasis on timing, dosage, and combination therapies [15].

Accurate and timely diagnosis of neonatal hypoxic-ischemic encephalopathy (HIE) is critical for the initiation of therapeutic interventions, particularly therapeutic hypothermia, which must begin within the first six hours of life for optimal efficacy. Diagnosis begins with a thorough clinical history and examination, focusing on perinatal events such as prolonged labor, umbilical cord accidents, or evidence of fetal distress. Criteria established by the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists include low Apgar scores, metabolic acidosis (pH <7.0), the need for resuscitation beyond 10 minutes, and signs of encephalopathy [16]. These clinical indicators, while essential, must be integrated with neurologic assessments and supportive investigations to confirm HIE and exclude differential diagnoses such as sepsis or metabolic disorders [17].

The Sarnat and Sarnat staging system is the most widely used clinical tool for assessing the severity of HIE. This system categorizes encephalopathy into three grades—mild, moderate, and severe—based on neurologic findings such as level of consciousness, muscle tone, reflexes, seizures, and autonomic function. While originally developed for term infants, modified scoring systems have been adapted for use in preterm populations [18]. Serial neurologic examinations are crucial in the first 72 hours to track the evolution of encephalopathy, which can fluctuate, particularly in moderate HIE. However, the system has limitations due to subjectivity and interobserver variability, especially in borderline cases [19].

Neuroimaging plays a pivotal role in confirming the diagnosis and delineating the extent of brain injury. Magnetic resonance imaging (MRI), especially with diffusion-weighted imaging (DWI), is the gold standard and is typically performed between days 4 and 7 of life. MRI provides detailed anatomical and functional insights, including patterns of injury that correlate with clinical severity and long-term outcomes. For example, involvement of the basal ganglia and thalamus is associated with severe outcomes in term infants, while watershed area injuries suggest milder, prolonged hypoxia [20]. Cranial ultrasound is more accessible and useful in unstable neonates, but it lacks the sensitivity of MRI in early-stage HIE [21].

Electroencephalography (EEG) and amplitude-integrated EEG (aEEG) are essential tools for assessing brain function and identifying subclinical seizures, which are common in HIE and often go undetected clinically. aEEG allows for continuous bedside monitoring and helps stratify the severity of encephalopathy based on background patterns. Severely abnormal patterns such as burst suppression or low-voltage tracing are associated with poor neurodevelopmental outcomes [22]. Standard multi-channel EEG remains the gold standard for seizure detection and provides a detailed evaluation of cortical function, although it may not always be readily available in all neonatal units [23].

Emerging diagnostic modalities are under investigation to enhance early and accurate detection of HIE. Biomarkers such as neuron-specific enolase (NSE), S100 calcium-binding protein B (S100B), and glial fibrillary acidic protein (GFAP) are being studied for their potential to reflect neuronal and glial injury in real time. While these biomarkers have shown promise in research settings, they are not yet integrated into routine clinical practice due to variability in sensitivity,

specificity, and timing of measurement [24]. Combining clinical scoring, imaging, electrophysiology, and potential biomarkers may offer a more holistic and individualized approach to diagnosis in the near future [25].

Umbilical cord blood gas analysis is a crucial diagnostic tool in assessing neonates for HIE. It provides immediate information about the acid-base status of the newborn at birth, reflecting the degree of hypoxia and acidosis experienced during labor. A pH value less than 7.0 and a base deficit greater than 12 mmol/L are indicative of significant asphyxia and are associated with an increased risk of HIE. This analysis aids in distinguishing between hypoxic-ischemic events and other causes of neonatal encephalopathy, facilitating timely intervention [16].

Examining the placenta can yield valuable insights into the etiology of HIE. Pathological findings such as infarctions, chorioamnionitis, or vascular malperfusion can suggest chronic intrauterine hypoxia or inflammatory processes contributing to neonatal brain injury. Identifying these placental abnormalities helps in understanding the timing and nature of the insult, which is essential for prognosis and counseling [17].

Amplitude-integrated EEG is a simplified, bedside method for continuous monitoring of cerebral activity in neonates. It is particularly useful in detecting subclinical seizures and assessing the severity of encephalopathy. Patterns such as burst suppression or low voltage on aEEG are associated with poor neurological outcomes. Early aEEG monitoring within the first six hours of life can guide decisions regarding therapeutic hypothermia and other interventions [18]. While aEEG provides valuable trend information, standard multi-channel EEG remains the gold standard for detecting and characterizing neonatal seizures. It offers detailed spatial and temporal resolution, allowing for precise localization and classification of seizure activity. This is critical for tailoring anticonvulsant therapy and assessing the risk of long-term neurological sequelae [19].

Neuroimaging plays a pivotal role in diagnosing and prognosticating HIE. Cranial ultrasound is often the first imaging modality used due to its accessibility and safety, though it has limited sensitivity in detecting early ischemic changes. MRI, particularly diffusion-weighted imaging (DWI), is more sensitive in identifying acute brain injuries and is typically performed between days 4 and 7 of life. MRI findings correlate with the severity of HIE and can predict neurodevelopmental outcomes [20].

Research into biochemical markers such as neuron-specific enolase (NSE), S100B protein, and glial fibrillary acidic protein (GFAP) is ongoing to enhance early diagnosis of HIE. Elevated levels of these biomarkers in blood or cerebrospinal fluid may reflect the extent of neuronal and glial injury. While promising, these biomarkers are not yet part of routine clinical practice due to variability in sensitivity and specificity [21].

In cases where the clinical presentation is atypical or when HIE is suspected without clear perinatal asphyxia, metabolic and genetic testing should be considered. Disorders such as inborn errors of metabolism or genetic syndromes can mimic or contribute to encephalopathy. Early identification of these conditions is crucial for targeted management and genetic counseling [22].

Beyond the Sarnat staging, other clinical scoring systems like the Thompson score have been developed to assess the severity of encephalopathy. These scores consider factors such as tone, level of consciousness, and seizure activity, providing a quantitative measure that can be tracked over time. They are useful in both clinical and research settings to standardize assessments [23].

An integrated approach combining clinical examination, neuroimaging, electrophysiological monitoring, and laboratory tests offers the most comprehensive assessment of HIE. This

multimodal strategy enhances diagnostic accuracy, guides therapeutic decisions, and improves

prognostication. It underscores the importance of a multidisciplinary team in managing affected neonates [24].

The window for initiating neuroprotective interventions like therapeutic hypothermia is narrow, typically within six hours of birth. Therefore, rapid and accurate diagnosis of HIE is imperative. Delays in recognition can result in missed opportunities for intervention, leading to worse neurological outcomes. Establishing protocols for early identification and management is essential in neonatal care units [25].

Management Strategies: Therapeutic Hypothermia and Beyond

Therapeutic hypothermia (TH) remains the only evidence-based intervention that effectively improves neurological outcomes in neonates with moderate to severe hypoxic-ischemic encephalopathy. It works by reducing cerebral metabolism and inhibiting secondary neuronal injury mechanisms including apoptosis, free radical production, and inflammatory cytokine release. The recommended protocol involves initiating cooling within 6 hours of birth, maintaining a core temperature of 33.5°C for 72 hours, and then gradually rewarming over 6–12 hours to avoid reperfusion injury [26].

The implementation of TH requires strict eligibility criteria to ensure benefit and minimize risk. These include a gestational age of ≥36 weeks, evidence of a perinatal hypoxic event (e.g., Apgar score ≤5 at 10 minutes, pH <7.0, base deficit ≥16 mmol/L), and signs of moderate to severe encephalopathy based on neurologic examination or amplitude-integrated EEG (aEEG) findings. If seizures or abnormal tone are noted, rapid initiation of TH is critical [27].

Whole-body cooling is currently favored over selective head cooling due to its simplicity, consistent temperature regulation, and improved efficacy in large multicenter trials such as the NICHD and TOBY studies. These studies demonstrated a significant reduction in death and major disability at 18 months in infants treated with TH compared to controls [28]. Whole-body cooling is achieved using servo-controlled cooling mattresses that automatically adjust based on the infant's core temperature, ensuring tight regulation.

Monitoring during TH is intensive and requires a multidisciplinary approach. Infants often experience bradycardia, coagulopathy, electrolyte imbalances, and thrombocytopenia during cooling. Serum electrolytes, glucose, lactate, and coagulation profiles should be assessed frequently. Supportive measures include fluid restriction, ventilatory support, and careful management of hypotension, which may occur due to decreased cardiac output associated with hypothermia [29].

The rewarming phase is crucial and must be conducted slowly—typically at 0.5°C per hour—to prevent sudden vasodilation, hypotension, and potential rebound seizures. Continuous monitoring of vital signs, neurologic status, and laboratory values is essential during this phase. Rewarming too quickly has been associated with adverse neurodevelopmental outcomes in some observational studies [30].

Despite the benefits of TH, nearly half of the infants still experience death or long-term disability, which has led to interest in adjunctive neuroprotective strategies. Erythropoietin (EPO), a hematopoietic growth factor with anti-apoptotic and anti-inflammatory properties, has shown promise in combination with TH in Phase II trials. EPO may enhance repair mechanisms and reduce brain injury in neonatal HIE [31].

Xenon gas, an inert noble gas, is another adjunctive therapy under investigation. It acts as an NMDA receptor antagonist and has demonstrated synergistic neuroprotective effects when combined with TH in animal models. Although early human studies are promising, technical challenges with administration and cost issues have limited widespread adoption [32].

Allopurinol, a xanthine oxidase inhibitor, has been proposed as an early intervention to reduce

oxidative stress during reperfusion following hypoxia. Some trials have shown a reduction in biomarkers of brain injury when administered prenatally to mothers or postnatally to infants, though conclusive evidence for improved outcomes is still lacking [33].

Magnesium sulfate, which stabilizes neuronal membranes and blocks NMDA receptors, is being explored as an adjunct to TH. Some small trials and animal studies have demonstrated its potential to reduce excitotoxic injury, but larger trials are needed before routine use can be recommended [34].

Stem cell therapy, particularly the use of umbilical cord blood-derived stem cells, represents a frontier in regenerative approaches to HIE. These therapies aim to promote repair of injured neural tissue and modulate the inflammatory response. While early-phase trials suggest safety and feasibility, efficacy data are still emerging [35].

More Updated Insights about Management Approach

The application of neuroprotective agents during the phase of primary energy failure remains largely experimental, with current strategies focusing on preconditioning cerebral tissue to tolerate reduced oxygen levels prior to a hypoxic-ischemic insult [34–38]. However, cerebral preconditioning is still poorly understood and currently not applicable in human clinical settings. Most novel therapeutic approaches aimed at mitigating secondary energy failure in hypoxic-ischemic encephalopathy (HIE) are designed to address several key mechanisms: reducing energy depletion, inhibiting glutamate release, enhancing glutamate reuptake, antagonizing glutamate receptors, suppressing inflammation, and interrupting downstream intracellular signaling cascades [39]. Promising emerging interventions include moderate therapeutic hypothermia, erythropoietin, umbilical cord blood-derived hematopoietic stem cell transplantation, antiepileptic agents (such as topiramate and phenobarbital), xenon gas, docosahexaenoic acid (DHA), and cannabinoid receptor agonists. These therapies are under investigation both as monotherapies and in combination with hypothermia or other modalities, aiming for synergistic benefits to enhance neurodevelopmental outcomes in affected neonates. Nevertheless, the precise mechanisms by which these therapies exert their neuroprotective effects remain to be fully elucidated.

Moderate Hypothermia

Among the most well-established and widely studied interventions for neonatal HIE is moderate hypothermia. This therapy is postulated to confer neuroprotection by attenuating oxidative stress and glutamate excitotoxicity, reducing cerebral oxygen consumption, and limiting apoptotic pathways [40]. In preclinical studies, moderate hypothermia has demonstrated significant preservation of neuronal integrity in vulnerable brain regions, including the parasagittal and lateral cortices, striatum (part of the basal ganglia), CA1 region of the hippocampus, and thalamus, when compared to untreated control models [41]. (Refer to Figure 3 for anatomical localization of affected brain regions.)

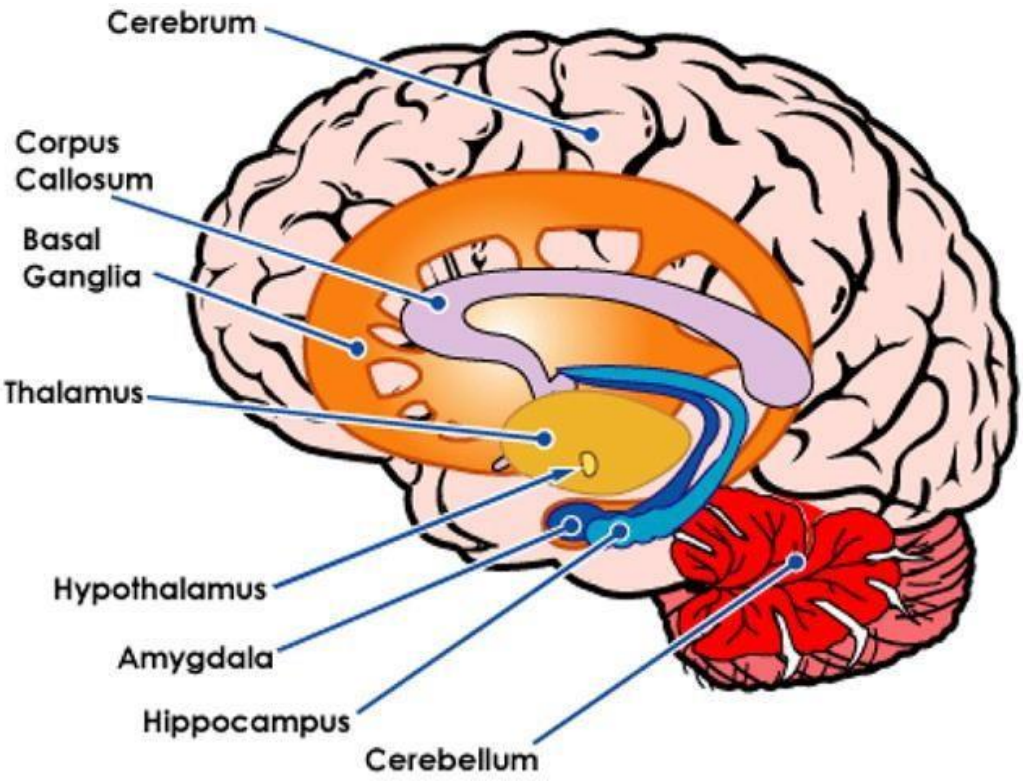

Figure 3: Location of Brain Structures Impacted by Treatments [41].

Hypothermia Therapy

Therapeutic hypothermia can be administered through either selective head cooling or whole-body cooling techniques in neonates [42]. This approach involves reducing the infant's core body temperature to a range between 33°C [43] and 36.5°C [44], typically maintained for 48 to 72 hours, followed by gradual rewarming to minimize the risk of complications such as hypotension. A meta-analysis by Shah involving 1,440 neonates across 13 randomized trials compared outcomes between infants receiving therapeutic hypothermia and those managed with standard care. The findings indicated that hypothermia initiated within the first six hours of life in infants with post-asphyxial hypoxic-ischemic encephalopathy (HIE) significantly decreased the incidence of mortality, moderate-to-severe neurodevelopmental impairment, cerebral palsy, severe visual impairment, cognitive deficits, and psychomotor delays at 12 months of age [42]. A separate meta-analysis of 767 infants from the CoolCap, NICHD, and TOBY trials assessed long-term outcomes at 18 months. The results demonstrated a significant reduction in mortality, severe disability, cerebral palsy, profound neurodevelopmental delay, and blindness among infants treated with hypothermia, although no improvement was observed in rates of deafness [46]. Despite these encouraging outcomes, approximately 30% of survivors who underwent therapeutic hypothermia still exhibited major neurodevelopmental impairments by 18 months of age. Notably, infants with moderate HIE showed a significant reduction in mortality and disability, whereas those with severe HIE did not experience a similar benefit [46]. These findings underscore that while moderate hypothermia improves outcomes in certain neonates, it remains insufficient as a standalone intervention, highlighting the need for adjunctive therapies to enhance neurodevelopmental outcomes.

Erythropoietin

Erythropoietin (EPO) is a glycoprotein hormone primarily known for its role in erythropoiesis [47]. Although it is predominantly produced by the kidneys, EPO is also synthesized by astrocytes, neurons, and oligodendrocytes in the vicinity of neural injury [49]. In neonatal animal models of hypoxic-ischemic brain injury, EPO receptor expression significantly increases within the first 24 hours following the insult, whereas endogenous EPO levels rise only modestly [50]. This limited elevation may be attributed to the inhibitory effects of pro-inflammatory cytokines [51] and reactive oxygen species [52], both of which are prevalent during the secondary phase of energy failure. The localized upregulation of EPO and its receptors suggests a potential endogenous neuroprotective response aimed at limiting neural injury [53].

The precise mechanisms through which exogenous EPO confers neuroprotection remain incompletely defined. However, proposed mechanisms include inhibition of neuronal apoptosis within the hippocampal CA1 region; attenuation of glial activation in the corpus callosum, thereby reducing glial scarring that hinders axonal regeneration [54]; suppression of primary brain edema by modulating aquaporin-4 (AQP4) water channels in astrocytes exposed to glutamate toxicity [56]; and reduction of infarct volume following injury [57].

Erythropoietin (EPO) in Clinical Trials

The therapeutic potential of erythropoietin (EPO) in neonates with hypoxic-ischemic encephalopathy (HIE) is currently under investigation in clinical trials. Administration of EPO at doses of 300 or 500 U/kg within the first 48 hours of life, followed by alternate-day dosing for a period of two weeks, was associated with a significant reduction in neurodevelopmental disability at 18 months when compared to controls [58]. Notably, this reduction in mortality and disability was observed predominantly in infants with moderate HIE, with no significant benefit reported in those with severe HIE [58]. In a separate study, early administration of a higher EPO dose (2500 U/kg) within 4–6 hours of birth for a total of five doses demonstrated improved neurologic outcomes at 6 months of age compared to control infants with HIE [59]. Despite these promising results, none of the EPO dosing regimens have yet demonstrated a significant reduction in overall mortality.

Although potential adverse effects of repeated EPO administration include hypersensitivity reactions, venous thrombosis, hypertension, electrolyte imbalances, and renal or hepatic dysfunction, such complications were not observed in the current clinical trials involving neonates with HIE. Longitudinal follow-up is essential to determine whether the neurodevelopmental benefits of EPO persist into later childhood. Further studies are also needed to assess whether combined use of moderate hypothermia and EPO can synergistically reduce mortality and long-term disability in this vulnerable population.

Umbilical Cord Blood Stem Cell Transplantation

Hematopoietic stem cell transplantation using umbilical cord blood is an emerging experimental therapy for neonates with HIE. Human umbilical cord blood contains mesenchymal and endothelial progenitor cells. The first successful umbilical cord blood transplant was performed in 1989 for a child with a genetic disorder. In the context of hypoxic-ischemic brain injury, stem cell therapy appears to exert neuroprotective effects through several mechanisms: decreasing neuronal death in the basal ganglia (but not in the cerebral cortex), inhibiting apoptosis in the basal ganglia, reducing lesion volume, and suppressing microglial activation, thereby limiting inflammation [62–64].

In neonatal animal models, administration of human umbilical cord blood within three hours following a hypoxic-ischemic event led to improved sensorimotor reflexes during the first post-

injury week when compared to controls [62]. A phase I clinical trial is currently underway,

allowing infants with a history of moderate to severe HIE to receive up to four infusions of autologous, volume-reduced cord blood cells. The number of infusions is contingent on the available quantity of cord blood. As the study is still enrolling participants, results are not yet available [65]. Continued research is needed in both animal models and human infants to better understand the mechanisms and long-term benefits of stem cell-based interventions.

Antiepileptic Medications

Antiepileptic drugs are being investigated as potential neuroprotective agents in HIE due to the overlap in molecular pathways activated by hypoxic-ischemic injury and seizures [47]. These agents are being evaluated both as standalone therapies [66] and in conjunction with therapeutic hypothermia [67]. Schubert et al. examined the efficacy of topiramate in neonatal animal models of HIE by comparing different dosing regimens: a loading dose of 20 mg/kg followed by 10 mg/kg/day (TMP-10), a loading dose of 50 mg/kg followed by 20 mg/kg/day (TMP-20), and a control group. The results showed no significant differences in seizure frequency between groups. However, animals in the TMP-20 group exhibited significantly reduced neuronal damage, while those in the TMP-10 group showed increased injury in the temporoparietal cortex, suggesting a dose-dependent effect of topiramate [66].

Another study evaluated the combined use of phenobarbital with hypothermia initiated at either 1 or 3 hours post-insult. Although the timing of hypothermia initiation did not influence outcomes, the groups receiving phenobarbital in combination with hypothermia demonstrated reduced brain injury and increased brain volumes compared to controls [67]. In one of the initial clinical trials assessing the safety of combining oral topiramate with therapeutic hypothermia in neonates with HIE, no adverse effects attributable to topiramate were observed [68]. However, this study did not evaluate long-term behavioral or cognitive outcomes [68]. Further research is essential to determine the long-term neurodevelopmental impact of early antiepileptic therapy and to clarify whether such treatments confer additive benefits when combined with hypothermia.

Xenon

Xenon, an inert anesthetic gas capable of crossing the blood-brain barrier, is believed to exert neuroprotective effects by antagonizing the glycine binding site of NMDA receptors, thereby reducing excitotoxic neurotransmitter activity [71]. By inhibiting excess glutamate from activating NMDA receptors and reducing the release of excitatory neurotransmitters, xenon attenuates stimulation of NMDA, AMPA, and kainate receptors. In neonatal animal models, administration of 50% xenon post-hypoxic-ischemic insult resulted in reduced injury in the cortex, white matter, hippocampus, basal ganglia, and thalamus compared to untreated controls [72].

Further studies have explored the combined effect of xenon and therapeutic hypothermia. When both treatments were initiated within 3 hours of injury, outcomes in neonatal models were similar to those of non-injured controls in both short- and long-term assessments [73]. Thoresen et al. investigated the effect of xenon timing, comparing immediate xenon therapy for 1 hour followed by 3 hours of hypothermia versus xenon initiated at 2 hours post-insult alongside immediate hypothermia. Results indicated no significant histopathological differences in key brain structures between the two regimens [74]. However, the efficacy of xenon administered with a 2-hour delay for a prolonged 3-hour duration in conjunction with hypothermia has yet to be evaluated.

Despite promising preclinical results, the clinical adoption of xenon is limited by concerns over cost and feasibility, as xenon costs approximately $10 per liter. To address these challenges, Chakkarapani et al. developed a single-use, closed-circuit xenon delivery system compatible with neonatal ventilators and endotracheal tubes [75]. In piglet models weighing approximately 1800 grams, the system allowed minimal xenon consumption (<$2/hour), due to the gas's low solubility and efficient retention following initial loading [75]. Importantly, xenon use did not adversely affect physiological parameters such as heart rate and blood pressure, suggesting a favorable safety profile for potential clinical application [75].

Docosahexaenoic Acid (DHA)

Docosahexaenoic acid (DHA) is a long-chain polyunsaturated omega-3 fatty acid predominantly sourced from fish, fish oil, and eggs [76]. Maternal dietary intake of DHA is currently being evaluated for its potential neuroprotective role in neonatal hypoxic-ischemic encephalopathy. DHA has been shown to inhibit apoptotic pathways, attenuate oxidative stress [77], and reduce inflammatory responses in the striatum and hippocampus following hypoxic-ischemic injury [78]. In neonatal animal studies, administration of DHA four hours prior to hypoxic insult significantly reduced histopathological damage, including hemispheric volume loss and hippocampal injury [76]. Moreover, treated animals exhibited notable improvements in sensorimotor function compared to untreated controls [76]. Nevertheless, further research is necessary to determine the long-term neurobehavioral effects and clinical efficacy of DHA supplementation before it can be recommended as a standard therapeutic intervention.

Cannabinoid Agonists

Endogenous cannabinoids play a vital role in modulating a range of physiological processes including motor function, cognition, learning and memory, appetite regulation, suckling behavior, and immune responses [79]. Their effects are primarily mediated through two receptor subtypes: cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2). Although the precise mechanisms through which cannabinoid agonists confer neuroprotection remain incompletely understood, they are hypothesized to exert their effects by inhibiting apoptosis, suppressing glutamate release, and attenuating neuroinflammatory responses [80].

In neonatal animal models subjected to severe hypoxic-ischemic insult, administration of the cannabinoid agonist WIN-55212 was associated with preservation of neuronal structure in surviving cells, with morphological features comparable to those observed in non-injured controls. Moreover, the number of viable neurons in the hippocampus and cortex was similar between the cannabinoid-treated and control animals [81]. Magnetic resonance imaging (MRI) studies further revealed that, although mild cerebral atrophy and ventricular enlargement were present in the cannabinoid-treated group, the degree of injury was significantly less than that observed in untreated controls, who demonstrated substantial cortical atrophy and marked reduction in neuronal density [81]. These findings support the potential neuroprotective role of cannabinoid agonists in neonatal hypoxic-ischemic brain injury. However, additional research is warranted to elucidate their mechanisms of action and to evaluate the safety and efficacy of translating these findings to human neonates.

Conclusion

Hypoxic-ischemic encephalopathy (HIE) remains one of the most critical complications associated with term birth, with limited preventive and therapeutic options currently available While the etiology of the hypoxic-ischemic insult may vary, the resultant brain injury primarily stems from impaired cerebral perfusion and diminished oxygen delivery to neural tissues The pathophysiology of HIE is generally divided into phases of primary and secondary energy failure,

with the latent period between these phases representing the optimal window for therapeutic

intervention Most novel therapeutic strategies under investigation focus on mitigating the effects of secondary energy failure. However, many of these emerging modalities have undergone limited testing in human neonates, and the extent to which findings from neonatal animal models can be reliably translated into clinical practice remains uncertain. Nevertheless, the continued pursuit of effective preventive and therapeutic measures is imperative to improve neurodevelopmental outcomes and reduce long-term disability in affected infants.

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