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A REVIEW OF NEONATAL HYPOXIC ISCHEMIC ENCEPHALOPATHY A NEUROLOGICAL DISORDER

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ABSTRACT

Hypoxia is a condition characterized by a deficiency of oxygen in the body or a specific organ or tissue, leading to various physiological and pathological effects. HIE is particularly common in newborns, known as Neonatal Hypoxic Ischemic Encephalopathy (NHIE). Intrapartum hypoxic events are a major contributor to neonatal mortality, accounting for approximately one in five neonatal deaths worldwide, with an estimated 717,000 deaths in recent decades. Hypoxic Ischemic Encephalopathy (HIE) is a leading cause of long-term neurological disability in neonates and adults due to inadequate blood and oxygen supply to the brain. Several factors like perinatal hypoxia, hemodynamics, poor perfusion rate, placental abnormalities, labour and multiple organ dysfunctions are included in the development of disorder. Understanding the underlying brain damage mechanisms is crucial for early detection and development of effective treatment strategies for high - risk patients. This review begins by discussing HIE, emphaisaising the broad array of other causes for neonatal encephalopathy, the epidemiology, neurologic presentations, diagnostics, and therapeutic strategies for HIE.

Keywords: *Hypoxia, Neonatal, Encephalopathy, Neurological ischemia*

INTRODUCTION

Hypoxic Ischemic Encephalopathy (HIE) is the primary etiology of chronic neurological impairment in both newborns and adults. HIE accounts for around 15% to 35% of all newborn encephalopathy cases in late preterm and full-term infants.[1,2] The phrase "neonatal encephalopathy" merely describes the neurological condition of the infant, being indifferent to the underlying etiology. There are an estimated 2 to 6 cases of neonatal encephalopathy for every 1000 full-term babies[3]. Encephalopathy in newborns is a wide term for brain malfunction that shows up as a change in mental status and an abnormal neurological exam. Hypoxic ischemic Encephalopathy is a specialized diagnostic that only applies when a newborn has encephalopathy which is known or strongly suspected to be caused by a lack of

oxygen and blood flow [4]. Altered mental status (including agitation, decreased responsiveness, lethargy, or stupor), respiratory depression, aberrant tone and/or movements, abnormal reflexes, and seizures. People sometimes use NE (Neonatal Encephalopathy) and HIE (Hypoxic-Ischemic Encephalopathy) to talk about a full-term baby who has an abnormal neurological exam at delivery and signs of perinatal hypoxic-ischemic encephalopathy [4]. Physicians who care for neonates must be familiar with the numerous causes of this condition. Approximately 24% of such patients die in the neonatal intensive care units (NICU). Of the surviving newborns about 10–20% have cerebral palsy, about 40% have eye sight or hearing loss and motor and behavioural damages are diagnosed in the form of epilepsy, global developmental delay and autism [5,6].

CLASSIFICATION

Hypoxia-ischemic encephalopathy (HIE) is a form of brain damage that occurs when an infant's brain does not receive enough oxygen and blood. It is divided into three grades [7] The classification was based on the sympotoms like level of consciousness, spontaneous activity, muscle tone, posture, stretch reflexes, reflex actions, cognition, and occulo vetibular and autonomic functions like respiratory rate and pupil reflexes etc.

a. **Mild HIE** – Baby might be a bit drowsy or fussy but typically does well with little or no lasting issues.

b. **Moderate HIE**: The baby may be unable to move, feed, or breathe easily and may require special care. Some long-term issues may occur.

c. **Severe HIE:** The baby has serious issues such as seizures, diminished reflexes, or comas. A long-term disability or even death is highly probable.

EPIDEMIOLOGY

The effect of hypoxic ischemic encephalopathy in various countries ranges about 1.5-2.5 per 2000 births . Though neonatal encephalopathy (NE) has historically been the cause of around 1 million infant fatalities yearly, the prevalence is significantly higher in developing and low- and middle-income nations. NE was responsible for 11% of mortality in children under five in 2019 (567,000 deaths, 95% UI: 476,000–673,000), according to recent estimates [8,9]. There are several detrimental neurological outcomes that can arise from hypoxic-ischemic encephalopathy (HIE), including cerebral palsy (CP), cognitive, neurodevelopmental, and neuromotor impairments, epilepsy, hearing and vision impairments, as well as intellectual, behavioral, and social disorders [10].In its severe form, HIE is strongly associated with increased neonatal mortality. A variety of maternal, fetal, placental, perinatal, and neonatal factors may contribute to its onset, and the condition can develop before, during, or after birth [12,13].

The incidence of HIE is reported to range between 1 and 8 per 1000 live births in developed nations, whereas in underdeveloped regions it may reach up to 26 per 1000 live births. Mortality has been estimated at 10% among infants with moderate HIE and as high as 85% in those with severe HIE. Likewise, long-term neurological disabilities were observed in approximately 30% of moderate cases and 75% of severe cases[14]. Globally, more than 750,000 infants are believed to develop moderate to severe HIE annually, with over 400,000 of them suffering permanent neurodevelopmental impairment. Consequently, HIE is recognized as a leading cause of early-life disability and accounts for nearly one-tenth of the global disability-adjusted life years (DALYs)[15].

A study conducted at tertiary care centre in Bhilai, chattisgarh on 180 babies admitted with birth defects asphyxia among them 33 babies had abnormal cranial findings has reflected hypoxic ischemia[16]. Likewise, a study carried out at NICU Jaipur on 52 infants has reported with hypoxic ischemia revealed the prevalence of this disorder[17]. Studies carried out at National neonatal collaborative multicentre cohort study and Nalanda medical college, Hospital,

Patna also reported similar hypoxic cases in infants. Overall, the incidences of this disease were found to be frequent and some found to be common occurrence in many of the infants.

CLINICAL SIGNS

Damage to the brain and associated neurological structures like neuroglia, white and grey matter is noticed in the disease. Half of newborns with HIE pass away in their early years, and 25% of those who survive develop long-term neurological aftereffects and disabilities, such as cerebral palsy, seizures, and learning and intellectual problems. abnormal EEG patterns and changes in mental state, such as drowsiness, agitation, or stupor. The affected group of people also exhibit abnormal reflexes, respiratory depression, cognitive impairment, and motor impairment[18,19] . Blue or pale colour of the skin along with organ dysfunction can be noticed in the severe cases. Metabolic acidosis can alter the pH of the blood. Ischemic changes can be identified while evaluation of brain tissues. This disorder is also characterised with low birth weight and gestational periods Mostly children are associated with seizures and intracerebral haemorrhages [20]. The need to spend in the NICU for prolonged period can be noticed and, in some instances, deaths are even reported. Approximately 40–50% of people who have survived moderate to severe HIE have neurodevelopmental disorders, including as intellectual disability and cerebral palsy. [22, 21]

- Hypoxia for one minute can cause convulsions, Unconsciousness and abolished pupillary reflex.
- Hypoxia for two minutes can develop mydriasis, the abolition of corneal reflex
- After five minutes Damage to the brain cortex that cannot be reversed
- 15 minutes later Permanent harm to the brain stem and spinal cord

PATHOPHYSIOLOGY

The manifestations of HIE include brain dysfunction and the exact cause is still not identified. While the exact cause is not always identified. Hypoperfusion and insufficient oxygen supply to neuronal cells was found to be the major cause of the disease. Occurrence of this event during the maturation of the brain can cause the HIE. The manifestations of perinatal HIE in early postnatal life include abnormal fetal heart rate tracings, poor umbilical cord gases (pH < 7.0 or base deficit ≥ 12 mmol/L), low APGAR scores, presence of meconium stained fluid, or the need for respiratory support within the first several minutes of postnatal life[23,24]. Several factors like cord prolapse, uterine rupture, abruptio placenta, placenta previa, maternal hypotension, breech presentation, or shoulder dystonia might be the reasons for the occurrence of HIE. The disorder seems to be multifactorial in which many of the factors seems to impair cerebral blood flow and oxygen delivery to the brain. The disorder was associated with loss of primary and secondary energy systems in the brain. Primary energy failure occurs as a result of the initial reduction of cerebral blood flow[25,26]. The impairment of cerebral blood flow leads to decreases in oxygen and glucose, which leads to significantly less energy (adenosine triphosphate (ATP) and increased lactate production. The lack of ATP in cell impairs many mechanisms which maintain the cell integrity. Secondary energy failure phase occurs 6 to 48 hours after the initial injury. The exact mechanisms of secondary energy failure remain unclear but appear to be related to oxidative stress, excitotoxicity, and inflammation[27,28]. The pathophysiological mechanisms of the HIE is associated with the development of necrosis and the release of inflammatory mediators which were found to be the crucial factors for the development of HIE. From the literature survey it was noticed that immature are associated with apototic neuronal death and necrotic cell death was predominated in mature brains[29]. There is a imbalance between hemodynamics and pulmonary circulations which can cause hypotension metabolic acidosis hypotension, and maintenance of adequate ventilation. Sometimes organ dysfunctions like renal failure. Though oxygen deprivation is the major cause consequent reperfusion injury often deteriorates the brain metabolism by increasing the oxidative

stress damage. A large excess of ROS will straight forwardly change or degenerate cell macromolecules, like membranes, proteins, lipids, and DNA, and lead to a cascading inflammatory reaction, and protease secretion. There even causes increase in extracellular glutamate, excessive activation of glutamate receptors (excitotoxicity), increase in cytosolic calcium (Ca^{2+}), is observed along oxidative stress. The seriousness of the HIE depends upon the duration of the event encephalopathy and severity of hypoxia like mild, acute and chronic hypoxia[30,31]. Miscellaneous factors can include maternal infection, medication or substance use, hypertensive disorders (pregnancy-induced hypertension, preeclampsia, chronic hypertension or HELLP syndrome), maternal obesity, birth trauma and abnormalities on antenatal ultrasound, or history of recurrent miscarriages or consanguinity or a family history of genetic disorders[32,33].

CLINICAL DIAGNOSIS

A thorough examination of the mother's health and family background, the pregnancy, the labor, and the delivery of the borne child. Fetal heart rate anomalies that are compatible with exposure to hypoxemia during birth should be ruled out, as should perinatal sentinel episodes (such as placental abrusion, shoulder dystocia, and umbilical cord prolapse).Supervision of the APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) score help in diagnosis of the disease APGAR scores less than ≤5 at 10 min after birth and being encephalopathic soon after birth suggest hypoxia-ischemia (HI) as the likely cause for the neonatal encephalopathy[34,35]. In most incidences babies with HIE are born with less weight and gestational age. General neuralogical examinations must be performed to confirm the incidence of the disease. An electroencephalogram (EEG) or amplitude integrated EEG (aEEG) showing aberrant brain activity is appropriate for confirming the presence and severity of encephalopathy, as can a clinical neurological examination (such as the Sarnat neuro exam or Thompson score)[36].

Neurological findings of HIE

Neurodevelopmental results are delayed when cognitive and behavioral difficulties are linked to structural abnormalities of the brain, such as decreased brainstem capacity, increased ventricular size, and decreased corpus callosum volume. The thalamus and basal ganglia's abnormal signal intensities are a substantial predictor of severe NHIE and poor neurodevelopmental outcomes between 18 and 24 months [37, 38]. Lesions in these deep brain areas are important markers of aberrant neurodevelopment. Additionally, MRI studies showed notable alterations, such as anomalies in axonal structures like the corpus callosum and decreased white matter integrity. Basal ganglia and thalamic changes were reported and found as the reason for motor impairment in HIE. The earlier literature also revealed the changes in signal intensity of the HIE brains. The same was revealed in the study conducted on 57 infants[39]. One study demonstrated that T1-weighted MRI can help distinguish hypoxic-ischemic cerebral changes from normal myelination in neonates by comparing signal intensities across brain regions. Infants with HIE showed higher signal intensity in the posterolateral putamen and peri-Rolandic cortex, and lower intensity in the posterior limb of the internal capsule and corona radiata. These regional differences provided good predictive value for identifying hypoxic-ischemic injury, highlighting the vulnerability of myelinated neurons[40]. MRI studies also showed lesions in the neocortex involving the deeper regions of the brain. gradual loss of neurons at the pontine level of the corticospinal tract, as well as hyperintensity in the ipsilateral internal capsule and cerebral peduncle, as well as declines in the apparent diffusion coefficient (ADC). This studies also make evident of characteristic lesions in the Basal ganglionic thalamic regions of brain which lead to motor impairment in HIE group of people. The CT-scan studies of the brain showed the loss of grey and white matter differentiation along with cerebral edema. Even diffuse

densities are observed at different regions of hippocampus, cerebrum, cerebellum and thalamus. CT studies also show reversal sign in severe cases particularly observed in children[41,42].

ADULT CASE REPORT OF HIE

Hypoxic-ischemic encephalopathy (HIE) is a common and serious neurological condition in adults.This neurovascular and neurometabolic illness has even happened in adults, resulting in hypotension, cardiac arrest with successful resuscitation, and carbon monoxide poisoning. There is a large body of literature showing the neurological, cognitive, behavioral, and psychosocial consequences of hypoxic ischemic brain injury (HIBI). Parkinsonism, dystonia, seizures, a reduction in processing speed, memory, executive function, and depression have all been described in this patient population. According to the literature, a large number of adult cases have been reported with HIE. Both the males and females were affected the ratio is more in males compared to females which may be due to smoking and alcohol abuse and related to cardiac diseases. The occurrence of this disease globally was found to be 86 percentage and deaths are reported in almost 65 percent of the cases. Studies carried out Germany, USA. Canada, in respective tertiary care hospitals has witnessed the incidence of the disease in adults. A cohort study conducted at the National Rehabilitation Centre reported the occurrence of the disease in adults aged 18–35 years[43,44].

THERAPIES AND PREVENTIVE MEASURES

Therapies under new development for Neonatal HIE

XENON

Xenon is an odourless noble gas used as an anaesthetic with strong neuroprotective effects in hypoxic – ischemic encephalopathy (HIE). At concentration below 50%, it can reduce brain injury, especially when combined with therapeutic hypothermia. Xenon works mainly by blocking NMDA receptors, preventing excitotoxicity, and activating potassium channels, while also promoting antiapoptotic and protective protein. It has been shown effective in cell, rodent, and pig models, but its clinical use is limited by high cost, scarcity, and the need for specialized closed-circuit delivery systems. In preclinical studies, xenon up-regulates anti-apoptotic proteins (Bcl2) and the Bcl-xl mitochondrial membrane molecule, modulates pro-inflammatory cytokinel levels (TNF-a), thus decreasing inflammatory, and increases growth factor (VEGF), leading to reduce cell death and enhanced repair. Xenon combined with TH in a P7 rat HI model improve behavioural outcomes assessed through staircase tests and open fields tests, demonstrating enhanced cognitive and motor function. This influencing recovery mechanisms in various neurological conditions[45].

GLUCOCORTOCOIDS

Glucocorticoids, which regulate function such as blood pressure, immunity, metabolism, and inflammation, have also demonstrated neuroprotective potential neonatal hypoxic – ischemic (HI) brain injury when administered intracerebroventricularly or intranasally. A protective, randomised, double-blind, placebo-controlled phase 1/2 trail (NCT02700828) evaluated the effect of low-dose hydrocortisone (0.5mg/kg) in asphyxiated newborns with volume – resistant hypotension undergoing hypothermia therapy. Participant received four doses over 24hours, alongside conventional inotropic support, for up to 72hours. The results showed that a significantly higher proportion of infants in the hydrocortisone group achieved at least a 5mmgHg rise in mean arterial pressure within two hours compared to placebo (94% vs. 58%, p=0.02). Hydrocortisone also reduced the need for inotropes suggesting its efficacy in stabilizing blood pressure during hypothermia treatment in HIE neonates[46].

TOPIRAMATE

An authorized anti-epileptic medication with neuroprotective properties topiramate (TPM). It works by antagonizing glutamate receptors, increasing the inhibitory effect of GABA receptors, and selectively blocking voltage- dependent sodium channel. TPM has demonstrate promise as a possible treatment for seizures in neonate with HIE, despite its primary use as an adjuvant drug for other safe and effective it's for treating neonatal HIE[47].

Neurodegenerative Therapies for Hypoxic -ischemic Encephalopathy

Current treatments for hypoxic ischemia episodes are inadequate in preventing neurological outcomes, highlighting the need for safe and effective therapeutics to restore impaired tissue function. The new approach aims to create neurodegenerative treatments, such as levodopa, to enhance dopamine and alleviate motor symptoms in HIE. Physical and occupational therapy, including exercises, gait training, and assistive devices, can improve functional independence and quality of life. The FDA approved four cholinesterase inhibitors (ChE-Is) and one NMDA receptor antagonist for treating Alzheimer's disease. Current ChE-Is include donepezil, rivastigmine, and galantamine. Research suggests that they can boost cognitive performance [48].

Mesenchymal stem cells-based therapy

Mesenchymal stem cells (MSCs) can self-renew and specialize into bone, cartilage, and fat cells. They originate from embryonic stem cells. Beyond this, show neurodegenerative, antiapoptotic, antioxidant, and immunomodulatory effects, mainly through releasing growth factors like VEGF, Bfgf, NGF, BDNF, and anti-inflammatory effects, cytokines. Preclinical studies in cell cultures and animals have shown that MSCs promote neural stem cell growth, increases neuronal survival, and enhance brain repair after hypoxic-ischemic injury for example, MSCs from human umbilical cord blood improved neural survival in rat brain region, while hypoxic precondition of MSCs boosted their migration to injury sites, reduced cell death, and activated repair pathway, leading function recovery[49].

NEUROTROPHIC FACTOR DERIVED FROM BRAIN

The neurotrophic factor derived from brain is a neurotropic that help nerve cell survives, grow, and change their synaptic structure. The two types of neurotrophic factors are of two types: pro brain neurotrophic derived factor and mature brain neurotrophic derived factor. They have a stronger affinity for a specific receptor; pro-BNDF specifically binds to the p75 neurotrophic receptor (p75), which causes proapoptotic signals. Mature BNDF exhibits a greater affinity for the tropomyosin-related kinase receptor type-B (Tridi), which triggers survival signals through the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) and phosphatidylinositol 3-kinase/akt pathways. The expression of BDNF, ITI receptors, and enzymes involved in BNDF processing rises in the ipsilateral zone of the lesion after a hypoxic-ischemic event, suggesting that BNDF contributes to HIE recovery. Neuroregeneration is a key goal in treating HIE. Brain - derived neurotropic factor (NDF) has been shown to promote neurite regeneration invitro by enhancing neuronal adhesion and forming growth cone -like structure. In HIE models, BNDF increased syntax in – 1b expression, which supports vesicles, exocytosis, and reduced voltage – dependent anion of channel protein 1(VDCA1), both contributing to neuron survival. In animal studies, intraventricular administration of BNDF with epidermal growth factor (EGF) boosted new neuron formation in the subventricular zone and striatum, increased B-3 tubulin expression in the neostriatum, and improved motor performance compared to control[50].

Gonadotrophin – Releasing hormone Agonist

A decapeptide called GnRH is generated by hypothalamus neurons and stimulates the pituitary gland to create and secrete follicle-stimulating hormone and luteinizing hormone, two essential hormones for mammalian reproduction. Because GnRH has a half-life of less than 10 minutes, GnRH receptors are known to function as both autocrine and paracrine regulators in different tissues. A member of the G-protein coupled receptor family, the GnRH receptor is primarily expressed in the adenohypophysis but has also been identified in the hippocampus, spinal cord, anterior cingulate cortex, motor cortex, lateral septal nucleus, amygdala, and hypothalamus. Due to its immunomodulatory and neuroregenerative qualities, GnRH agonist may be a new treatment for HIE. It has also been found in breast, prostate, and adrenal tissue cancer cells. [51]

DISCUSSION

This article offers a comprehensive overview of Hypoxia Induced Encephalopathy (HIE), but a deeper discussion is needed to highlight the complexities of this condition. The occurrence of the disease is multifactorial like genetic, lifestyle, cardiovascular and respiratory challenges were included. Symptoms of the disease overlap each other affecting the precise diagnosis of the disease. HIE can leads to the number of the neurological disorders like parkinsonism, Alzheimer's, cerebral palsy[21]. The disorder can cause life threatening conditions like unconsciousness, coma, The article emphasizes that HIE leads to long-term neurological disabilities like cerebral palsy and developmental delays[5]. This underscores that HIE is not just an acute event but a chronic condition requiring lifelong management. The vulnerable population of this group consists of mostly neonates. Many of the perinatal causes gestational age and predetermined births, labour and caesarean procedures can indulge in the development of HIE in neonates. Neonates with APGAR scores less than 7 are considered as more risk for the development of HIE[23]. The severity of the disease is more there is a Global impact the incidence of HIE in full-term live infants ranges from 1 to 8 per 1000, and even in developed countries, the incidence is 1.5 to 2 per 1000. Around 400,000 babies develop neurodevelopmental disorders caused by HIE worldwide each year. HIE affects about 100,000 infants each year in China[8,36]. This emerging condition can be avoided by avoiding the risk factors at gestational age with regular diagnosis and supervision of physician. The disorder can be acute and chronic several conditions like diabetes, obesity, tumours, cardiac obstructions and hemodynamic properties of blood flow can induce the chronic HIE. The use of therapeutic agents like neurodegenerative modulators, physical and occupational therapies nay improve the condition. Certain neurotransmitters like dopamine deficiency must be treated with agents like levodopa and administration of corticosteroids can prevent inflammatory mediators of the disease. Symptomatic treatment in HIE is always a challenging factor. Improvement in motor coordination, cognition and memory can be done by enhancing the levels of neurotransmitters and signal intensities. The review of novel therapies like Xenon and stem cell-based treatments is promising. However, a significant gap exists between preclinical research and widespread clinical application due to challenges like cost and safety concerns. For example, while mesenchymal stem cells show promise in animal models for neuroregeneration, their use in humans is still in early stages. Therefore, current standard of care, primarily therapeutic hypothermia, remains the cornerstone of treatment for moderate to severe HIE. Future discussions should focus on how these new therapies can be integrated with existing treatments to improve patient outcomes, rather than replacing them entirely.

CONCLUSION

In conclusion Neonatal hypoxic ischemia is a neurodegenerative disorder found to be most frequent occurrence in the Neonates. The disease has a global impact on the neonates with high rate of the death. Multiple factors like perinatal status, genetic and neonatal traumatic conditions were included. It is one of the major factors for poor neuro development, abnormal behaviour, lack of cognition, memory, intelligence and some motor disabilities in the neonates.

REFERENCES

[1]. O'Neill S, Wayman M, Schofield I. Hypoxic Brain Injury. CPD Anaesthesia. 2023 Jan 27;9(3):157–9.

[2]. Cetinkaya M. Neuroprotective treatment options for neonatal hypoxic-ischemic encephalopathy: Therapeutic hypothermia and beyond. Global Pediatrics. 2024 Sep 1;9:100223.

[3]. Russ JB, Simmons R, Glass HC. Neonatal Encephalopathy: Beyond Hypoxic-Ischemic Encephalopathy. Neoreviews. 2021;22(3):e148–62.

[4]. Ranjan AK, Gulati A. Advances in Therapies to Treat Neonatal Hypoxic-Ischemic Encephalopathy. Journal of Clinical Medicine 2023, Vol 12, Page 6653. 2023 Oct 20;12(20):6653.

[5]. Giliberti A, Frisina AM, Giustiniano S, Carbonaro Y, Roccella M, Nardello R. Autism Spectrum Disorder and Epilepsy: Pathogenetic Mechanisms and Therapeutic Implications. J Clin Med [Internet]. 2025 Apr 1 [cited 2025 Sep 26];14(7):2431. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11989834/

[6]. Deveci MF, Turgut H, Alagöz M, Kaya H, Gökçe IK, Özdemir R. Mortality related factors on hypoxic ischemic encephalopathic patients treated with therapeutic hypothermia: an 11-year single-center experience. Turk J Med Sci [Internet]. 2022 [cited 2025 Sep 26];52(3):796. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10390112/

[7]. Mohamed Soliman IH, Mohamed Eladl AA. Hypoxic-Ischemic Encephalopathy in Neonates: Current Concepts in Diagnosis and Management. Cuestiones de Fisioterapia. 2024 Aug 20;53(02):342–65.

[8]. Shu J, Liu L, Yuan M, Ma M, Yang J. Paradigm shifts in neonatal hypoxic-ischemic encephalopathy therapeutics: a four-decade bibliometric exploration of emerging therapeutic dimensions (1985–2024). Front Pediatr [Internet]. 2025 Jul 28 [cited 2025 Sep 26];13:1611345. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC12336269/

[9]. Vidavalur R, More K, Bhutani VK. Assessment of Global Burden due to neonatal encephalopathy: An economic evaluation. Semin Fetal Neonatal Med. 2024 Dec 1;29(6):101560.

[10]. Cetinkaya M. Neuroprotective treatment options for neonatal hypoxic-ischemic encephalopathy: Therapeutic hypothermia and beyond. Global Pediatrics. 2024 Sep 1;9:100223.

[11]. Shabani N, Proverbio AM. Neonatal hypoxia: impacts on the developing mind and brain. Frontiers in Cognition. 2025 Feb 28;4:1565759.

[12]. de Souza Lima B, Sanches APV, Ferreira MS, de Oliveira JL, Cleal JK, Ignacio-Souza L. Maternal-placental axis and its impact on fetal outcomes, metabolism, and development. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2024 Jan 1;1870(1):166855.

[13]. Sokou R, Lianou A, Lampridou M, Panagiotounakou P, Kafalidis G, Paliatsiou S, et al. Neonates at Risk: Understanding the Impact of High-Risk Pregnancies on Neonatal Health. Medicina (B Aires) [Internet]. 2025 Jun 1 [cited 2025 Sep 27];61(6):1077. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC12194930/

[14]. Korf JM, McCullough LD, Caretti V. A narrative review on treatment strategies for neonatal hypoxic ischemic encephalopathy. Transl Pediatr [Internet]. 2023 Aug 1 [cited 2025 Sep 27];12(8):1552–71. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10485647/

[15]. Victor S, Rocha-Ferreira E, Rahim A, Hagberg H, Edwards D. New possibilities for neuroprotection in neonatal hypoxic-ischemic encephalopathy. Eur J Pediatr [Internet]. 2022 Mar 1 [cited 2025 Sep 27];181(3):875–87. Available from: https://pubmed.ncbi.nlm.nih.gov/34820702/

[16]. Sudhakar C, Jindal P. Profile of hypoxic ischemic encephalopathy in newborns in a tertiary care centre of Bhilai, Chhattisgarh, India. Int J Contemp Pediatrics [Internet]. 2018 Oct 22 [cited 2025 Sep 27];5(6):2032–7. Available from: https://www.ijpediatrics.com/index.php/ijcp/article/view/1949

[17]. Singh S, Vangala AR. Incidence and Outcomes of Hypoxic-Ischemic Encephalopathy in NICU Admissions: A Retrospective Cohort Study from Jaipur, India. Journal of Contemporary Clinical Practice [Internet]. 2025 Jan 30 [cited 2025 Sep 27];11:219–21. Available from: https://jccpractice.com/article/incidence-and-outcomes-of-hypoxic-ischemic-encephalopathy-in-nicu-admissions-a-retrospective-cohort-study-from-jaipur-india-883/

[18]. Allen KA, Brandon DH. Hypoxic Ischemic Encephalopathy: Pathophysiology and Experimental Treatments. Newborn Infant Nurs Rev [Internet]. 2011 Sep [cited 2025 Sep 27];11(3):125. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC3171747/

[19]. Back SA. Cerebral white and gray matter injury in newborns: New insights into pathophysiology and management. Clin Perinatol [Internet]. 2014 Mar [cited 2025 Sep 27];41(1):1. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC3947650/

[20]. Busl KM, Greer DM. Hypoxic-ischemic brain injury: Pathophysiology, neuropathology and mechanisms. NeuroRehabilitation [Internet]. 2010 [cited 2025 Sep 27];26(1):5–13. Available from: https://www.researchgate.net/publication/41405282_Hypoxic-ischemic_brain_injury_Pathophysiology_neuropathology_and_mechanims

[21]. Eriksson Westblad M, Löwing K, Grossmann KR, Blennow M, Lindström K. Long-term motor development after hypothermia-treated hypoxic-ischaemic encephalopathy. European Journal of Paediatric Neurology. 2023 Nov 1;47:110–7.

[22]. Babbo CCR, Mellet J, van Rensburg J, Pillay S, Horn AR, Nakwa FL, et al. Neonatal encephalopathy due to suspected hypoxic ischemic encephalopathy: pathophysiology, current, and emerging treatments. World Journal of Pediatrics [Internet]. 2024 Nov 1 [cited 2025 Sep 27];20(11):1105. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11582131/

[23]. Moolchandani G, Moolchandani J, Iqbal N, Turab SM, Kashif M, Farooq L. Hypoxic Ischemic Encephalopathy: Think Outside the Box. 2022 [cited 2025 Sep 27]; Available from: https://dx.doi.org/10.17582/journal.pjz/20220531050513

[24]. Torbenson VE, Tolcher MC, Nesbitt KM, Colby CE, EL-Nashar SA, Gostout BS, et al. Intrapartum factors associated with neonatal hypoxic ischemic encephalopathy: A case-controlled study. BMC Pregnancy Childbirth [Internet]. 2017 Dec 11 [cited 2025 Sep 27];17(1). Available from: https://www.researchgate.net/publication/321734297_Intrapartum_factors_associated_with_neonatal_hypoxic_ischemic_encephalopathy_A_case-controlled_study

[25]. Alake O, Hardman S, Chakkarapani E. Managing hypoxic ischaemic encephalopathy in term newborn infant. Paediatr Child Health. 2018 Sep 1;28(9):399–404.

[26]. Lichtblau1 CH, Raffa2 S, Assadi3 K, Warburton4 C, Meli5 G, Gorman6 A. Hypoxic Ischemic Brain Injury in the Developing Brain. Int J Phys Med Rehabil [Internet]. 2023 Sep 7 [cited 2025 Sep 27];11(7):1–4. Available from: https://www.longdom.org/open-access/hypoxic-ischemic-brain-injury-in-the-developing-brain-102869.html

[27]. Maïza A, Hamoudi R, Mabondzo A. Targeting the Multiple Complex Processes of Hypoxia-Ischemia to Achieve Neuroprotection. Int J Mol Sci [Internet]. 2024 May 1 [cited 2025 Sep 27];25(10):5449. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11121719/

[28]. Shankaran S. Hypoxic-ischemic encephalopathy and novel strategies for neuroprotection. Clin Perinatol [Internet]. 2012 Dec [cited 2025 Sep 27];39(4):919–29. Available from: https://www.researchgate.net/publication/233723147_Hypoxic-ischemic_Encephalopathy_and_Novel_Strategies_for_Neuroprotection

[29]. Wu L, Chang E, Zhao H, Ma D. Regulated cell death in hypoxic-ischaemic encephalopathy: recent development and mechanistic overview. Cell Death Discov [Internet]. 2024 Dec 1 [cited 2025 Sep 27];10(1):277. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11167026/

[30]. Burd I, Welling J, Kannan G, Johnston M V. Excitotoxicity as a Common Mechanism for Fetal Neuronal Injury with Hypoxia and Intrauterine Inflammation. Adv Pharmacol [Internet]. 2016 [cited 2025 Sep 27];76:85–101. Available from: https://www.researchgate.net/publication/299451860_Excitotoxicity_as_a_Common_Mechanism_for_Fetal_Neuronal_Injury_with_Hypoxia_and_Intrauterine_Inflammation

[31]. Jurcau A, Ardelean AI. Oxidative Stress in Ischemia/Reperfusion Injuries following Acute Ischemic Stroke. Biomedicines [Internet]. 2022 Mar 1 [cited 2025 Sep 27];10(3):574. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC8945353/

[32]. Chakkarapani E, de Vries LS, Ferriero DM, Gunn AJ. Neonatal encephalopathy and hypoxic-ischemic encephalopathy: the state of the art. Pediatr Res [Internet]. 2025 [cited 2025 Sep 27]; Available from: https://www.researchgate.net/publication/390153850_Neonatal_encephalopathy_and_hypoxic-ischemic_encephalopathy_the_state_of_the_art

[33]. Sandoval Karamian AG, Mercimek-Andrews S, Mohammad K, Molloy EJ, Chang T, Chau V, et al. Neonatal encephalopathy: Etiologies other than hypoxic-ischemic encephalopathy. Semin Fetal Neonatal Med. 2021 Oct 1;26(5).

[34]. Downes KL, Grantz KL, Shenassa ED. Maternal, Labor, Delivery, and Perinatal Outcomes Associated with Placental Abruption: A Systematic Review. Am J Perinatol [Internet]. 2017 Aug 1 [cited 2025 Sep 27];34(10):935. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC5683164/

[35]. Simon L V., Shah M, Bragg BN. APGAR Score. StatPearls [Internet]. 2024 Mar 19 [cited 2025 Sep 27];1–6. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470569/

[36]. Chen X, Chen H, Jiang D. Maternal and Fetal Risk Factors for Neonatal Hypoxic-Ischemic Encephalopathy: A Retrospective Study. Int J Gen Med [Internet]. 2023 [cited 2025 Sep 27];16:537. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC9936872/

[37]. Khan S, Aldawood YO, Kazi N, Sideeque S, Ansari N, Mohammed H, et al. Brain structural and functional alteration in movement disorders: A narrative review of markers and their dynamic changes. NeuroMarkers [Internet]. 2025 Sep 24 [cited 2025 Sep 27];100130. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2950588725000953

[38]. Mcmorris T, Mikhailovna Bazanova O, Shabani N. Neonatal hypoxia: impacts on the developing mind and brain. 2025;

[39]. Wisnowski JL, Wintermark P, Bonifacio SL, Smyser CD, Barkovich AJ, Edwards AD, et al. Neuroimaging in the term newborn with neonatal encephalopathy. Semin Fetal Neonatal Med. 2021 Oct 1;26(5).

[40]. Liauw L, Palm-Meinders IH, Van Der Grond J, Leijser LM, Le Cessie S, Laan LAEM, et al. Differentiating Normal Myelination from Hypoxic-Ischemic Encephalopathy on T1-Weighted MR Images: A New Approach. AJNR Am J Neuroradiol [Internet]. 2007 Apr [cited 2025 Sep 27];28(4):660. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7977352/

[41]. Levison SW, Rocha-Ferreira E, Kim BH, Hagberg H, Fleiss B, Gressens P, et al. Mechanisms of Tertiary Neurodegeneration after Neonatal Hypoxic-Ischemic Brain Damage. Pediatr Med [Internet]. 2022 Aug 1 [cited 2025 Sep 27];5:28. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10438849/

[42]. Van Cauter S, Severino M, Ammendola R, Van Berkel B, Vavro H, van den Hauwe L, et al. Bilateral lesions of the basal ganglia and thalami (central grey matter)—pictorial review. Neuroradiology [Internet]. 2020 Dec 1 [cited 2025 Sep 27];62(12):1565–605. Available from: https://link.springer.com/article/10.1007/s00234-020-02511-y

[43]. Wei R, Jing D, Meng X, Wei H. Hypoxic-ischemic encephalopathy induced cognitive decline secondary to upper gastrointestinal bleeding: a case report. World J Emerg Med [Internet]. 2023 [cited 2025 Sep 27];14(4):335. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10323498/

[44]. Mukundan M, Sethi PP, Meena MK, Kant R. Clinico-Radiological Dissociation in a Patient with Hypoxic Ischemic Encephalopathy. Journal of Medical Sciences and Health [Internet]. 2020 Dec 1 [cited 2025 Sep 27];6(3):74–8. Available from: http://jmsh.ac.in/clinico-radiological-dissociation-in-a-patient-with-hypoxic-ischemic-encephalopathy

[45]. Shi Q, Rammes G, Wang P, Xia C, Mou F, Zhu J, et al. Effects of Xenon on the Developing Brain: Current Insights from Pre-clinical and Clinical Studies. J Integr Neurosci [Internet]. 2025 Mar 1 [cited 2025 Sep 27];24(3):26388. Available from: https://www.imrpress.com/journal/JIN/24/3/10.31083/JIN26388/htm

[46]. Concepcion KR, Zhang L. Corticosteroids and perinatal hypoxic-ischemic brain injury. Drug Discov Today [Internet]. 2018 Oct 1 [cited 2025 Sep 27];23(10):1718. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC6440944/

[47]. Pearl NZ, Babin CP, Catalano NT, Blake JC, Ahmadzadeh S, Shekoohi S, et al. Narrative Review of Topiramate: Clinical Uses and Pharmacological Considerations. Adv Ther. 2023 Sep 1;40(9):3626–38.

[48]. Muller AJ, Marks JD. Hypoxic ischemic brain injury: Potential therapeutic interventions for the future. Neoreviews [Internet]. 2014 [cited 2025 Sep 27];15(5):e177. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC4148699/

[49]. Wang Y, Wang H, Tan J, Cao Z, Wang Q, Wang H, et al. Therapeutic effect of mesenchymal stem cells and their derived exosomes in diseases. Molecular Biomedicine [Internet]. 2025 Dec 1 [cited 2025 Sep 27];6(1):34. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC12137892/

[50]. Colucci-D'amato L, Speranza L, Volpicelli F. Neurotrophic Factor BDNF, Physiological Functions and Therapeutic Potential in Depression, Neurodegeneration and Brain Cancer. Int J Mol Sci [Internet]. 2020 Oct 2 [cited 2025 Sep 27];21(20):7777. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7589016/

[51]. Marques P, Lages ADS, Skorupskaite K, Rozario KS, Anderson RA, George JT. Physiology of GnRH and Gonadotrophin Secretion. Endotext [Internet]. 2024 Oct 15 [cited 2025 Sep 27]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK279070/

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