INTRAPARTUM ASPHYXIA AND NEONATAL HYPOXIC-ISCHEMIC ENCEPHALOPATHY: PATHOPHYSIOLOGICAL BASES, DIAGNOSIS, AND CLINICAL MANAGEMENT

ASFIXIA INTRAPARTO E ENCEFALOPATIA HIPÓXICO-ISQUÊMICA NEONATAL: BASES FISIOPATOLÓGICAS, DIAGNÓSTICO E MANEJO CLÍNICO

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Ramón Miguel Vargas-Vera[1], Martha Placencia-Ibadango[2], Jocelyn Maribel Alencastro-Placencia[3], Ana María Flores-Luna[4], César William Luciano Salazar[5], Paul Vilchez Castro[6], Lito Danny Campos-Carbo[7], Norma Matilde Erazo-Flores[8], Kathiuska Stefany Vargas-Silva[9], Allison Deyalit Mero-Sánchez[10]

ABSTRACT

Perinatal asphyxia and neonatal hypoxic-ischemic encephalopathy are among the leading causes of neonatal morbidity and mortality and long-term neurological disability worldwide. This condition results from impaired gas exchange leading to hypoxemia, hypercapnia, and metabolic acidosis, triggering a pathophysiological cascade characterized by cellular energy failure, excitotoxicity, oxidative stress, inflammation, and neuronal apoptosis. The incidence is higher in low- and middle-income countries, and its etiology is multifactorial, including intrapartum hypoxic events as well as prenatal and postnatal factors. Clinically, it manifests with altered level of consciousness, hypotonia or hypertonia, neonatal seizures, and multiorgan involvement. The Sarnat classification allows stratification of severity and helps

[1] Dr. Catholic University of Santiago de Guayaquil. University of Guayaquil.
E-mail: dr.ramonmiguelvargasvera@gmail.com Orcid: https://orcid.org/0000-0002-1922-8983
[2] Dr. University of Guayaquil. E-mail: martha.placenciai@ug.edu.ec
Orcid: https://orcid.org/0000-0003-3967-6166
[3] Bachelor's degree. Catholic University of Santiago de Guayaquil. E-mail: jocy.alencastro@gmail.com
Orcid: https://orcid.org/0009-0007-7759-0079
[4] Master's degree. General Hospital Monte Sinai. E-mail: anitaflores1984@gmail.com
Orcid: https://orcid.org/0009-0001-9210-5592
[5] Master's degree. National University of Tumbes. E-mail: clucianos@untumbes.edu.pe
Orcid: https://orcid.org/0000-0002-1329-4605
[6] National University of Tumbes. E-mail: pvilchezc@untumbes.edu.pe
Orcid:https://orcid.org/0000-0002-1435-5836
[7] Master's degree. University of Guayaquil. E-mail: lito.camposc@ug.edu.ec
Orcid: https://orcid.org/0000-0003-1327-2200
[8] Obstetrician. Centro Médico Servinatal, Fundación Somos Prevenir. E-mail: norera4@hotmail.com
Orcid: https://orcid.org/0000-0001-5933-4628
[9] Nurse practitioner. University of Buenos Aires. E-mail: kattvargas88@gmail.com
Orcid: https://orcid.org/0009-0008-3718-3329
[10] University of Guayaquil. E-mail: allison_mero@hotmail.com Orcid: https://orcid.org/0009-0002-0707-5526

guide prognosis. Diagnosis requires a multimodal approach integrating clinical assessment, blood gas analysis, electroencephalographic monitoring, and neuroimaging, with magnetic resonance imaging being the gold standard for detecting early brain injury. Treatment is based on intensive support and neuroprotective strategies, with early-initiated therapeutic hypothermia standing out as an intervention that reduces mortality and neurological sequelae in moderate to severe cases. However, therapeutic limitations persist, and new alternatives such as erythropoietin, melatonin, and cellular therapies are under investigation. Prognosis depends on clinical severity, neuroimaging findings, and electroencephalographic evolution. In conclusion, neonatal hypoxic-ischemic encephalopathy remains a significant clinical challenge, requiring timely prevention and comprehensive multidisciplinary management. Furthermore, long-term follow-up is essential to detect neurodevelopmental impairments and optimize rehabilitation interventions and comprehensive family support, improving functional outcomes in childhood.

Keywords: Perinatal Asphyxia. Hypoxic-Ischemic Encephalopathy. Therapeutic Hypothermia. Neuroprotection. Neonatal Seizures. Biomarkers.

RESUMO

A asfixia perinatal e a encefalopatia hipóxico-isquêmica neonatal constituem uma das principais causas de morbimortalidade neonatal e de incapacidade neurológica a longo prazo em nível mundial. Essa condição resulta de uma alteração das trocas gasosas, levando à hipoxemia, hipercapnia e acidose metabólica, desencadeando uma cascata fisiopatológica caracterizada por falha energética celular, excitotoxicidade, estresse oxidativo, inflamação e apoptose neuronal. A incidência é maior em países de baixa e média renda, e sua etiologia é multifatorial, incluindo eventos hipóxicos intraparto, bem como fatores pré-natais e pós-natais. Clinicamente, manifesta-se por alterações do nível de consciência, hipotonia ou hipertonia, convulsões neonatais e comprometimento multiorgânico. A classificação de Sarnat permite estratificar a gravidade e orientar o prognóstico. O diagnóstico requer uma abordagem multimodal que integra avaliação clínica, gasometria, monitorização eletroencefalográfica e neuroimagem, sendo a ressonância magnética o padrão-ouro para a detecção precoce de lesão cerebral. O tratamento baseia-se em suporte intensivo e estratégias de neuroproteção, destacando-se a hipotermia terapêutica iniciada precocemente como intervenção capaz de reduzir a mortalidade e as sequelas neurológicas em casos moderados e graves. No entanto, persistem limitações terapêuticas, motivo pelo qual novas alternativas, como eritropoetina, melatonina e terapias celulares, estão em investigação. O prognóstico depende da gravidade clínica, dos achados em neuroimagem e da evolução eletroencefalográfica. Em conclusão, a encefalopatia hipóxico-isquêmica neonatal continua sendo um desafio clínico relevante, exigindo prevenção oportuna e manejo multidisciplinar integral. Além disso, o seguimento a longo prazo é fundamental para detectar alterações do neurodesenvolvimento e otimizar intervenções de reabilitação e apoio familiar integral, melhorando os desfechos funcionais na infância.

Palavras-chave: Asfixia Perinatal. Encefalopatia Hipóxico-Isquêmica. Hipotermia Terapêutica. Neuroproteção. Convulsões Neonatais. Biomarcadores.

RESUMEN

La asfixia perinatal y la encefalopatía hipóxico-isquémica neonatal constituyen una de las principales causas de morbimortalidad neonatal y discapacidad neurológica a largo plazo a nivel mundial. Esta entidad resulta de una alteración del intercambio gaseoso que conduce a hipoxemia, hipercapnia y acidosis metabólica, desencadenando una cascada

fisiopatológica caracterizada por falla energética celular, excitotoxicidad, estrés oxidativo, inflamación y apoptosis neuronal. La incidencia es mayor en países de ingresos bajos y medios, y su etiología es multifactorial, incluyendo eventos hipóxicos intraparto y factores prenatales y posnatales. Clínicamente, se manifiesta con alteraciones del estado de conciencia, hipotonía o hipertonía, convulsiones neonatales y compromiso multiorgánico. La clasificación de Sarnat permite estratificar la gravedad y orientar el pronóstico. El diagnóstico requiere un enfoque multimodal que integra evaluación clínica, gasometría, monitoreo electroencefalográfico y neuroimagen, siendo la resonancia magnética el estándar de referencia para detectar lesión cerebral temprana. El tratamiento se basa en soporte intensivo y estrategias de neuroprotección, destacando la hipotermia terapéutica iniciada precozmente como intervención que reduce mortalidad y secuelas neurológicas en casos moderados y graves. No obstante, persisten limitaciones terapéuticas, por lo que se investigan nuevas alternativas como eritropoyetina, melatonina y terapias celulares. El pronóstico depende de la severidad clínica, hallazgos en neuroimagen y evolución electroencefalográfica. En conclusión, la encefalopatía hipóxico-isquémica neonatal continúa siendo un desafío clínico relevante, requiriendo prevención oportuna y manejo multidisciplinario integral. Asimismo, el seguimiento a largo plazo es fundamental para detectar alteraciones del neurodesarrollo y optimizar intervenciones de rehabilitación y apoyo familiar integral y mejorar resultados funcionales en la infancia.

Palabras clave: Asfixia Perinatal.Encefalopatía Hipóxico-Isquémica. Hipotermia Terapéutica. Neuroprotección. Convulsiones Neonatales. Biomarcadores.

1 INTRODUCTION

Perinatal asphyxia continues to be an important cause of neonatal morbidity and mortality and permanent neurological sequelae worldwide. It is estimated that hypoxic-ischemic encephalopathy (HIE) affects approximately 1–3 per 1000 live births in developed countries and a higher proportion in low- and middle-income countries(1,2). HIE represents one of the leading causes of childhood neurological disability, including cerebral palsy, developmental delay, epilepsy, and long-term cognitive disorders(3).

Despite advances in perinatal care, HIE continues to be a relevant public health problem, especially in low- and middle-income countries. Affected newborns present with a wide spectrum of clinical manifestations including altered level of consciousness, neonatal seizures, hypotonia, and autonomic dysfunction.

In recent decades, the understanding of the pathophysiology of hypoxic-ischemic brain injury has evolved considerably. Likewise, advances in neurophysiological monitoring and advanced neuroimaging techniques (4,5). Likewise, the introduction of therapeutic hypothermia has significantly modified the clinical management and prognosis of these patients (6,7).

The development of therapeutic hypothermia has represented the greatest advance in the treatment of this condition in recent decades; however, a considerable percentage of patients continue to have long-term neurological sequelae.

Definition of perinatal asphyxia

Perinatal asphyxia is defined as an alteration in gas exchange that produces hypoxemia, hypercapnia and metabolic acidosis, which can trigger multiple organ dysfunction(8). However, in modern clinical practice, the term neonatal encephalopathy associated with hypoxia-ischemia is preferred, since perinatal asphyxia alone does not necessarily imply brain injury(9).

Currently, the term neonatal encephalopathy associated with a hypoxic-ischemic event is preferred. According to the consensus of the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP), the diagnosis of neonatal encephalopathy related to intrapartum asphyxia requires the presence of several clinical and biochemical criteria, including severe metabolic acidemia, persistent low Apgar score, signs of moderate or severe neonatal encephalopathy, and evidence of multiorgan dysfunction (10).

In addition, the concept of sentinel hypoxic event is recognized, which describes acute obstetric events capable of producing severe fetal hypoxia, such as placental abruption, uterine rupture, umbilical cord prolapse or massive fetal-maternal hemorrhage.

1.1 SUGGESTED DIAGNOSTIC CRITERIA

The main criteria used include:

1. Severe metabolic acidosis in cord blood
2. Apgar score ≤5 at 10 minutes
3. Evidence of moderate or severe neonatal encephalopathy
4. Evidence of Multi-Organ Dysfunction

2 EPIDEMIOLOGY

The overall incidence of neonatal hypoxic-ischemic encephalopathy varies significantly according to the level of health development. In developed countries it is estimated at **1–3 per 1000 live births**, while in developing countries it can reach **5–10 per 1000 live births** (11).

Table 1

Region	Estimated incidence
Developed countries	1–3/1000 live births
Developing countries	5–10/1000 live births

Factors influencing the incidence:

- Access to obstetric care
- Intrapartum fetal monitoring
- Availability of neonatal intensive care units (12)

3 ETIOLOGY

Neonatal encephalopathy can be caused by multiple mechanisms.

Acute intrapartum hypoxic events

- Placental abruption
- Uterine rupture
- Umbilical cord prolapse
- Amniotic fluid embolism
- Massive fetal-maternal hemorrhage

Prenatal factors

- Placental insufficiency
- Intrauterine infections
- Fetal growth restriction

Postnatal factors

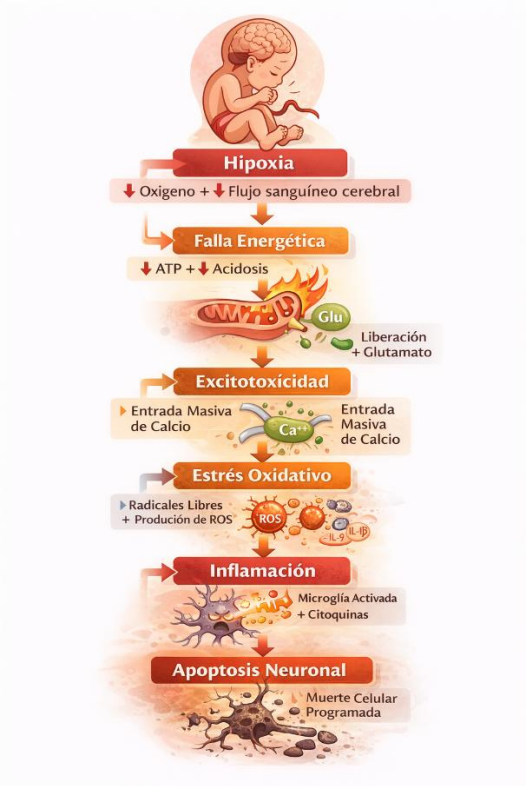
- Respiratory failure
- Neonatal sepsis
- Congenital heart disease

3.1 PATHOPHYSIOLOGY

Hypoxic-ischemic brain injury occurs as a result of reduced oxygen supply and cerebral blood flow. This process triggers a complex cascade of cellular and molecular events including energy depletion, excitotoxicity, free radical accumulation, inflammation, and neuronal apoptosis (13,14). (Fig. 1)

Figure 1

Pathophysiological cascade of hypoxic-ischemic encephalopathy



Source: Authors' elaboration based on Volpe (1), Davidson et al. (13) and Fleiss et al. (30).

The pathophysiology of HIE occurs in three main phases:

1. Primary phase (acute hypoxia)

It is characterized by:

- Decreased cerebral blood flow
- Reduced oxygen supply
- Cellular power failure
- Lactate Accumulation (15)

2. Reperfusion phase

Subsequently, it occurs:

- Glutamate-mediated excitotoxicity
- Massive intracellular calcium input
- Free radical generation

3. Secondary phase

Between **6 and 48 hours later**, a secondary phase of injury occurs characterized by:

- Glutamate-mediated excitotoxicity
- Massive intracellular calcium input
- Free radical production
- Activation of inflammatory cascades and neuronal apoptosis (16,17)

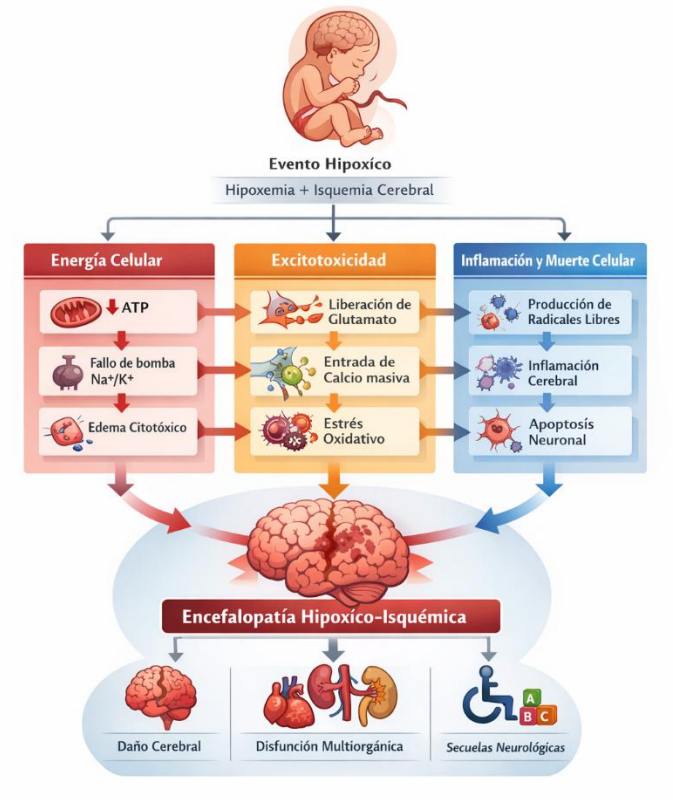
This period constitutes a **critical therapeutic window for neuroprotective interventions**, such as therapeutic hypothermia (6).

These processes can extend brain damage even after perfusion is restored.

Brain damage usually develops in two main phases. The primary phase occurs during the hypoxic-ischemic event and is characterized by cellular energy failure. Subsequently, a secondary phase of injury occurs, between 6 and 48 hours later, associated with oxidative stress, glutamate release and programmed neuronal death. This period represents a critical therapeutic window for neuroprotective interventions such as therapeutic hypothermia. Fig. 2)

Figure 2

Pathophysiology of perinatal asphyxia



Source: Adapted from Gunn and Bennet (29), Douglas-Escobar and Weiss (3), Davidson et al. (13)

4 CLINICAL MANIFESTATIONS

Neonatal hypoxic-ischemic encephalopathy is characterized by a constellation of neurological signs that appear in the first hours of life. These include altered level of consciousness, hypotonia or hypertonia, decreased primitive reflexes (18), breathing difficulties, and neonatal seizures.

4.1 CLASSIFICATION OF SARNAT

The most widely used clinical classification is the one proposed by **Sarnat and Sarnat**, which divides neonatal encephalopathy into three stages: mild, moderate, and severe (19). This classification is based on state of consciousness, muscle tone, motor activity, reflexes, and the presence of seizures. (Table 2)

Table 2

Clinical classification of neonatal hypoxic-ischemic encephalopathy according to Sarnat

Feature	Stage I (mild)	Stage II (moderate)	Stage III (severe)
Level of consciousness	Irritable	Lethargic	Stupor/coma
Muscle tone	Normal	Hypotonia	Sagging
Moro's Reflex	Over-the-top	Weak	Absent
Suction	Weak	Absent	Absent
Seizures	Rare	Frequently Asked	Variables
Duration	<24 h	2–14 days	Prolonged

Source: Adapted from Sarnat and Sarnat (19).

Clinical manifestations include:

Neurological

- Altered state of consciousness
- Hypotonia
- Neonatal seizures
- Absence of primitive reflexes

Systemic

- Respiratory failure
- Cardiac dysfunction
- Kidney failure
- Intestinal necrosis

Diagnostic evaluation

The diagnostic evaluation of newborns with suspected hypoxic-ischemic encephalopathy requires a multimodal approach that includes clinical evaluation, neurophysiological studies, and neuroimaging (20).(Table 2)

Amplitude integrated electroencephalogram (aEEG) is widely used for continuous monitoring of brain function in neonatal intensive care units. This technique allows detecting subclinical seizures and evaluating early neurological prognosis (21).

Regarding neuroimaging, brain magnetic resonance imaging is the most sensitive diagnostic method for detecting hypoxic-ischemic lesions. Diffusion sequences can identify brain damage in the first 24–48 hours of life (22).

In addition, several serum and cerebrospinal fluid biomarkers have been investigated, such as neuron-specific enolase, S100B protein, GFAP and UCH-L1, which could contribute in the future to the prognostic evaluation of these patients.

Diagnosis is based on a combination of clinical, biochemical, and neurophysiological criteria.

4.2 NEUROPHYSIOLOGICAL STUDIES

Amplitude-integrated electroencephalogram (aEEG) can detect cortical alterations and subclinical seizure activity, and is useful for early prognosis (22).

Neuroimaging

Brain ultrasound

- Useful for evolutionary tracking

MRI

It is the study of choice to evaluate the extent and location of brain damage.

Typical injuries include:

- Basal Nodes
- Thalamus
- White matter
- Cerebral cortex

Complementary exams

Arterial blood gases

- pH <7.0
- Base deficit >12 mmol/L

Electroencephalography (EEG/aEEG)

It allows detecting:

- Subclinical seizures
- Suppression-burst pattern

MRI

Diffusion brain MRI is currently the gold standard for evaluating neonatal brain injury.

Biomarkers

Biomarkers studied include:

- Neuronal Specific Enolase
- Protein S-100
- CK-BB
- Interleukin-6

These reflect neuronal damage and have prognostic value.

Table 3

Diagnostic evaluation in neonatal hypoxic-ischemic encephalopathy.

Study	Clinical utility
Blood gases	Confirmation of metabolic acidosis
EEG / aEEG	Brain Activity Assessment

Brain ultrasound	Initial assessment
MRI	Neurological prognosis

Source: Adapted from Rutherford (10), Lally and Montaldo (31) and Alderliesten (32

Multi-organ involvement

Perinatal hypoxic-ischemic aggression is not limited to the central nervous system. Various organs may be compromised due to the redistribution of blood flow during the asphyxial episode.

The most common manifestations include acute renal failure, myocardial dysfunction, persistent pulmonary hypertension of the newborn, liver disorders and metabolic disorders. Early identification of these complications is essential to optimize clinical management.

Perinatal asphyxia can cause multi-organ involvement, including:

Nervous System

- Encephalopathy
- Neonatal seizures

Renal system

- Oliguria
- Acute renal failure

Cardiovascular system

- Myocardial ischemia
- Ventricular dysfunction

Respiratory system

- Persistent pulmonary hypertension

Gastrointestinal system

- Ischemic enterocolitis

Hematology System

- Disseminated intravascular coagulation

4.3 TREATMENT

The management of newborns with hypoxic-ischemic encephalopathy is based on intensive support measures and neuroprotection strategies (23)

General measures include maintaining adequate oxygenation and ventilation, correcting metabolic disturbances, controlling blood pressure, and prompt treatment of neonatal seizures.

Therapeutic hypothermia is currently the standard treatment for newborns with moderate or severe HIE. This procedure involves reducing body temperature to

approximately 33–34 °C for 72 hours, starting within the first six hours of life. Various clinical trials have shown that this therapy reduces mortality and improves long-term neurological prognosis (7,25).

New neuroprotective strategies, including erythropoietin, inhaled xenon, melatonin, and cell therapies, are also being investigated, which could complement therapeutic hypothermia in the future.

General measures

- Adequate oxygenation
- Blood pressure control
- Correction of metabolic acidosis
- Blood Glucose Control
- Seizure treatment

Therapeutic hypothermia

Therapeutic hypothermia is the standard treatment for moderate and severe HIE.

Indications

- Gestational age ≥36 weeks
- Moderate or severe encephalopathy
- Start within the first 6 hours
- Protocol

Parameter	Value
Temperature	33–34 °C
Duration	72 hours
Reheating	gradual (0.5 °C/h)

- This treatment has been shown to reduce mortality and improve neurological disability

Emerging therapies

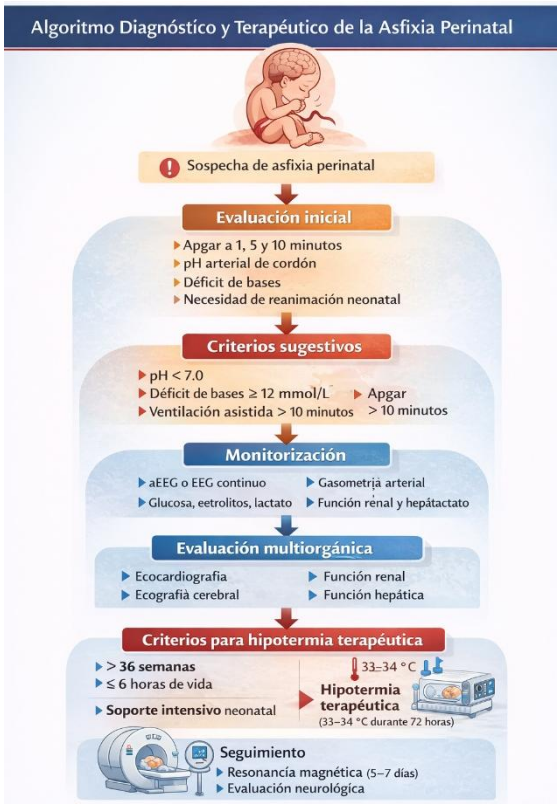
In current research:

- Erythropoietin
- Mesenchymal stem cells
- Inhaled xenon
- Melatonin
- Metabolic therapies

Clinical algorithm for the management of perinatal asphyxia

Figure 3

Diagnostic and therapeutic algorithm for neonatal hypoxic-ischemic encephalopathy



Source: Adapted from Laptook and Shankaran (7), Jacobs et al. (8), Massaro and Chang (14).

4.4 PROGNOSIS

The prognosis depends mainly on:

- *Degree of encephalopathy*
- *Neuroimaging findings*
- *Electroencephalographic evolution (26)*

The severity of the initial neurological involvement. Newborns with mild HIE usually have a favorable outcome, while those with moderate or severe forms are at increased risk of permanent neurological disability.

Brain MRI and early neurophysiological monitoring are fundamental tools for prognostic evaluation. Long-term follow-up is essential to detect neurological, cognitive, and motor developmental disorders.

Mortality in severe HIE can reach 50–75%, and most survivors have neurological sequelae (27).

Table 4

Grades of toxic ischemic encephalopathy

HIE Grade	Mortality	Neurological sequelae
Mild	<5%	Weird
Moderate	10–20%	Moderate disability
Severe	40–60%	frequent cerebral palsy

Recent studies show that 30–50% of survivors may have long-term cognitive deficits.

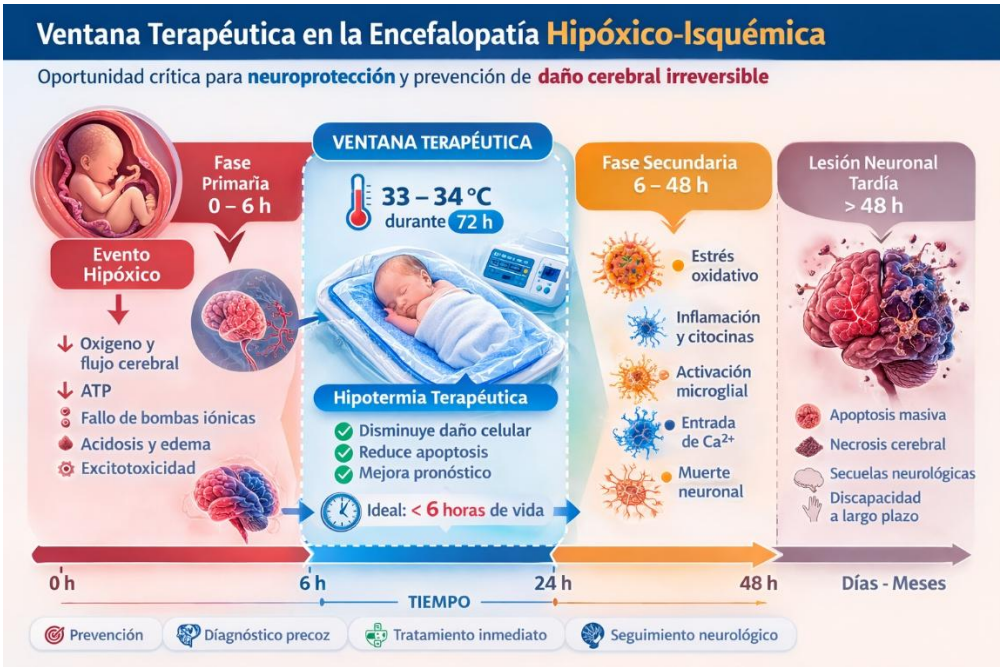
Neurological follow-up

Multidisciplinary follow-up is recommended:

- Pediatric Neurology
- Rehabilitation
- Early stimulation
- Neurodevelopmental Assessment (28)

Figure 4

Therapeutic window of hypoxic-ischemic encephalopathy"



Source: Gunn & Bennet, Nature Reviews Neurology.

Table 5

Multi-organ manifestations of perinatal asphyxia.

Organ	Demonstrations
Brain	Encephalopathy, seizures
Kidney	Oliguria, kidney failure
Heart	Myocardial dysfunction, ischemia
Lung	Persistent pulmonary hypertension
Liver	Transaminase elevation
Hematology	Coagulopathy

Source: Adapted from Perlman (33) and Graham et al. (4).

Table 6

Current criteria for neonatal therapeutic hypothermia.

Criteria	Parameter
Gestational age	≥ 36 weeks
Postnatal age	≤ 6 hours
Evidence of choking	pH ≤ 7.0 or BE ≥ 12
Neurological involvement	Moderate or severe HIE

Source: Adapted from Shankaran et al. (6), Laptook et al. (7) and Jacobs et al. (8).

New emerging biomarkers

You can add a modern section on:

Biomarkers under investigation:

- UCH-L1
- GFAP
- Neuron specific enolase
- S100B

These help to:

- Detect neuronal damage early
- Predict neurological prognosis

5 MEDICO-LEGAL IMPLICATIONS

Lawsuits for alleged obstetric negligence are common after the birth of a newborn with moderate to severe hypoxic-ischemic disease, associated with a risk of adverse outcome. In general terms, the family usually attributes these outcomes to a supposed lack of obstetric care to detect or intervene in a timely manner in the event of possible intrapartum asphyxia.

However, it is essential to consider that, in most cases, the time of onset, duration and susceptibility factors that determine the severity of hypoxic aggression remain unknown. Likewise, the perinatal criteria suggestive of asphyxia do not allow, by themselves, to establish with certainty an intrapartum origin of the brain injury. In fact, a significant proportion of newborns who meet criteria for perinatal asphyxia have a history prior to delivery that may have contributed to the development of hypoxic-ischemic encephalopathy (HIE).

Therefore, given the medico-legal, emotional and social implications associated with perinatal asphyxia, it is essential to carry out an exhaustive and comprehensive analysis of perinatal and postnatal data, including complementary studies, before establishing causal relationships.

Neuropathological studies allow the identification of the characteristic lesions of acute asphyxia in fatal cases, both in terms of their morphology and distribution; however, they may also show ischemic lesions of antenatal origin.

Ultimately, the birth of a child with perinatal asphyxia and an unfavorable outcome creates an emotionally charged situation in which the possibility of litigation for alleged obstetric or neonatal negligence often helps to distance the family from health professionals who could provide support and guidance.

Therefore, it is recommended that each institution establish mechanisms that facilitate parents' access to clear information, emotional support and adequate accompaniment, in order to reduce their feeling of isolation and better cope with the situation, establishing a causal relationship between intrapartum events and neurological damage, which is why it is required:

- Evidence of intrapartum acidosis
- Early neonatal encephalopathy
- Exclusion of other causes

6 CONCLUSIONS

Neonatal hypoxic-ischemic encephalopathy continues to represent a highly relevant clinical challenge in perinatal medicine, due to its important contribution to neonatal mortality and long-term neurological disability, including cerebral palsy, epilepsy, and cognitive disorders (33,36). Despite advances in its pathophysiological understanding, this entity remains complex and multifactorial, which makes it difficult to accurately identify the timing and cause of brain damage (34).

Advances in early diagnosis, particularly through neurophysiological monitoring and neuroimaging techniques, have allowed for better risk stratification and more timely decision-making in affected newborns (34, 38). In this context, therapeutic hypothermia has established itself as the standard of treatment, demonstrating a significant reduction in mortality and neurological disability in moderate to severe cases (34,35). However, its efficacy is not universal, and a considerable number of patients continue to have sequelae, which shows the need for additional therapeutic strategies (35).

In relation to prevention, it is essential to strengthen prenatal and intrapartum surveillance, as well as to optimize perinatal care systems to identify fetuses at risk early and act in a timely manner. Likewise, the standardization of diagnostic criteria and management protocols contributes to improving the quality of care and clinical outcomes (38).

On the other hand, the development of new neuroprotective therapies is a priority in current research. Several studies have explored pharmacological agents, cell therapies, and strategies aimed at modulating inflammation, oxidative stress, and excitotoxicity, with the aim of enhancing the effects of therapeutic hypothermia and improving neurological prognosis (35). However, many of these interventions are still in the experimental phase and require validation in high-quality clinical trials.

Finally, the approach to hypoxic-ischemic encephalopathy must be comprehensive and multidisciplinary, including not only acute management, but also long-term follow-up and neurological rehabilitation. This approach allows optimizing functional outcomes and providing adequate support to families, considering the medical, social, and emotional implications of this condition.

In conclusion, although significant advances have been made in the diagnosis and treatment of neonatal hypoxic-ischemic encephalopathy, important challenges remain in its prevention, management, and prognosis, which underscores the need to continue promoting research and innovation in this field.

Therefore, neonatal hypoxic-ischemic encephalopathy continues to represent a major clinical challenge in perinatal medicine. Advances in early diagnosis, neurophysiological monitoring, and the implementation of therapeutic hypothermia have significantly improved the prognosis of these patients (6,20).

Considering that prevention, timely diagnosis and the development of new neuroprotective strategies continue to be priority areas of research (29).

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