An Overview about Neonatal Hypoxic Ischemic Encephalopathy

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Abstract

Background: Hypoxic ischemic brain injury describes brain injury due to exposure to hypoxia and/ or ischemia as evidenced by biochemical [creatine kinase brain function (CK-BB)], electrophysiologic (EEG), neuroimaging (MRI and CT scan), or pathologic (postmortem examination) means. HIE is an important cause of permanent damage to CNS cells that may result in neonatal death or be manifested later as Cerebral Palsy (CP) or mental deficiency. 20 to 25 % of infants with HIE die in the neonatal period and 25-30% of survivors are left with permanent neurodevelopment abnormalities as cerebral palsy or mental retardation. Within minutes of the onset of total fetal hypoxia, bradycardia, hypotension, decreased cardiac output, and severe metabolic as well as respiratory acidosis occur. The initial circulatory response of a fetus is increased shunting through the ductus venosus, ductus arteriosus, and foramen ovale, with transient maintenance of perfusion of the brain, heart and adrenals in preference to the lung, liver, kidneys and intestine. Following initial resuscitation and stabilization, treatment of HIE is largely supportive and should focus on adequate ventilation and perfusion, careful fluid management, avoidance of hypoglycemia and hyperglycemia and treatment of seizures. Intervention strategies aim to avoid any further brain injury in these infants

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Introduction:

Hypoxic ischemic encephalopathy is the hypoxic ischemic brain injury as a result of perinatal asphyxia, HIE is the most important consequence of perinatal asphyxia and it is one of the serious neurologic problems of the perinatal period. Also, HIE is the single most important perinatal cause of neurological morbidity in both full –term and premature infant **(Ahearne et al., 2016)**.

Concerning definition of perinatal asphyxia , there is no single tool that can yield a precise definition, the American Academy of pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG) committee on maternal fetal medicine and newborn in 1996 defined certain criteria that must be present to confirm the occurrence of perinatal asphyxia (table 1) .'

Table (1): Essential criteria of perinatal asphyxia

1- Profound metabolic or mixed acedemia PH< 7 on an umbilical cord arterial blood sample.

2- Persistence of an Apgar score of 0 to 3 > 5 minutes.

3- Clinical neurologic sequelae in the immediate neonatal period.

4- Evidence of multiorgan system dysfunction in the immediate neonatal period.

(American Academy of Pediatrics (AAP) and American College of Obstetricians and Gynecologists (ACOG), 1996) and (2012).

HIE is an important cause of permanent damage to CNS cells that may result in neonatal death or be manifested later as Cerebral Palsy (CP) or mental deficiency. 20 to 25 % of infants with HIE die in the neonatal period and 25-30% of survivors are left with permanent neurodevelopment abnormalities as cerebral palsy or mental retardation **(Volpe, 2012).**

Risk factors:

Table 2 show biologic risk factors for asphyxia.

Table (2): Biologic risk factors for asphyxia

Maternal/prenatal	
Pre-eclamsia toxemia	Premature rupture of membranes
Smoking	Infection
Diabetes	Placental insufficiency
Chronic hypertension	Chronic illness such as cardiopulmonary
Substance abuse during pregnancy	disease and chronic renal failure
Injury during pregnancy	
Maternal age <15 or >35 years	
Intrapartum	
Abnormal fetal presentation	Abruptio placentae
Prolapsed cord	Placenta praevia
Umbilical cord occlusion	
Perinatal	

Prematurity/Post maturity	Respiratory distress syndrome
Growth retardation	Patent ductus arteriosus
Fetal distress (heart rate<100)	Intraventricular hemorrhge
Multiple births	Seizures
Polyhydraminos	Hyperglycemia/hypoglycemia
Congenital anomalies	Hyperthermia/hyopthermia
Meconium staining/aspiration	Hypercalcemia/hypocalcemia
Hyperbilirubinemia	
	Repetitive injures

(Aslam et al., 2014)

Risk factors for birth asphyxia were grouped into antepartum, intrpartum, and postnatal or infant variables **(Lundgren et al., 2018).**

Epidemiologic studies have shown that of all cases of neonatal encephalopathy, 69% had only antepartum risk factors, 25 % had both antepartum and intrapartum risk factors, 4% had evidence of only intrapatum hypoxia without identified preconception or antepartum had no identified risk factors. Thus, approximately 70% of neonatal encephalopathy is secondary to events arising before the onset of labor **(Tann et al., 2018)**.

Causes of HIE:

1) Antepartum causes:

The risk of newborn encephalopathy increased with increasing maternal age and decreased with increasing parity. Risk factors during pregnancy were maternal thyroid disease. Sever pre-eclampsia, moderate or severe bleeding a clinically diagnosed viral illness and placenta described at delivery as abnormal **(Odd et al., 2017).**

Intrapartum causes:

An association between neonatal asphyxia and intrauterine meconium release, operative delivery, breech delivery, oxytocin augmentation, cord complication and external compression to assist delivery was found. Abnormal fetal heart rate variability, repeated late deceleration irrespective of amplitude or repeated variable decelerations and no acceleration were associated with asphyxia (**Tchirikov et al., 2018).**

Infants exposed to intrapartum maternal fever had a three –fold increase in the risk of being diagnosed with seizure and a three and half –increased risk of being diagnosed with Birth asphyxia. Infants exposed to chorioamnionitis had a five-fold increased risk of being diagnosed with seizure and almost a sevenfold increased risk of being diagnosed **(Johnson et al., 2016).**

2) **Postnatal causes**

Condition in the neonatal period may be responsible for as much as 10% of HIE cases. These include congenital heart disease, severe pulmonary disease, sever recurrent apnea, and cardiac failure secondary to a large patent ductus arteriosus. The preterm infants more affected than the term infant **(Toso et al., 2014).**

Growth restriction was also strongly associated with the risk of newborn encephalopathy. Infants with low haemoglobin level are at increased risk for developing HIE and that low PH and Apgar scores may predict worse outcomes after birth asphyxia **(Nemati et al., 2018)**.

Initial hypoglycemia is an important-risk factor for perinatal brain injury, particularly in depressed term infants who require resuscitation and have sever fetal acidemia **(Rudolph, 2018)**.

Perinatal asphyxia:

Placental insufficiency is responsible for 90% of asphyxial insults that occur in the antepartum /intrapartum periods as a result of inability to provide oxygen and remove CO_2 and H^+ from the fetus .The reminder is postpartum secondary to pulmonary, cardiovascular or neurological insufficiency. Perinatal asphyxia could be exacerbated by any of the following conditions: impairment of maternal oxygenation, decrease of blood flow from mother to placenta or from placenta to fetus, impairment of gas exchange across placenta or in the fetal tissue and increase in fetal oxygen requirements **(Sehgal et al., 2018).**

Stoll and Kliegman (2004) divided the etiological factors of perinatal asphyxia into:

A- Fetal hypoxia**.**

B- Neonatal hypoxia.

Fetal hypoxia:

It may result from maternal or placental or umbilical cord factors:

Maternal factors include all factors that interfere with maternal oxygenation such as cardiac, pulmonary, neurological disease, maternal hypotension that may complicate spinal anesthesia or that result from compression of vena cava and aorta by gravid uterus **(Brennan et al., 2016).**

Maternal vascular disease, drug abuse, blood disease, pre-eclampsia and severe anemia leads to relative hypoxia and consequently may predispose to lowered fetal oxygen tension resulting in fetal and consequently neonatal compromise **(Heimer et al., 2018).**

Neonatal hypoxia:

It may result from:

1- If anemia is sever enough to lower the oxygen content of the blood to a critical level due to sever hemorrhage or hemolytic disease.

2- Shock severe enough to interfere with oxygen transport to vital cells from adrenal medulla, intraventriular hemorrhage, overwhelming infection or massive blood loss.

3- A deficit in arterial oxygen saturation resulting from failure to breath adequately postnatally due to cerebral defect, nacrosis or injury.

4- Failure of oxygenation of adequate amount of blood as result of severe forms of cyanotic congenital heart disease or pulmonary disease. **(Ceyran et al., 2015)**

Clinical Picture and sequelae of HIE

Sarnat and Sarnat (1976) established three clinical categories of HIE. Each of these stages corresponds to progressively more severe level of injury. The stages of HIE correlate fairly well with the severity of neonatal injury and outcome clinical picture and sequelae. Stage I represents the transient, but the reversible phase of neuronal damage; stage II may or may not be reversible damage; and those with stage III HIE definitely have some irreversible destruction of neurons.

Table (3): Modified staging of HIE

Stage of HIE	Neurological characteristics
I	Lasts less than 24 hour hyperalerteness, uninhibited Moro and stretch reflexes, sympathetic effects, normal EEG.
II	Obtundation, hypotonia, strong distal extremity flexion and multifocal seizures.
III	Stuporous, suppressed brainstem and autonomic functions.

(Gomella et al., 2016)

Mild HIE (grade I):

These infants show no alteration in the level of consciousness but appear to be hyperalert, they spend more time awake and restless, often with staring eyes. They show excessive response to stimulation and they are jittery with spontaneous or exaggerated Moro reflex. Suckling reflex is often weak and the infants need encouragement to complete feeds. Passive limb tone is normal. When newborn is held in a sitting position, some head lag is noticeable but the tone of neck extensors is relatively increased compared with the flexors. Limb reflexes are normal or slightly increased but sustained ankle clonus may be detectable. Clinically, apparent seizures do not occur **(Gomella et al., 2016).**

Moderate HIE (grade II):

The main feature of this grade is seizures and lethargy with reduction in spontaneous movements. Seizures usually occur in the second day of life but may be seen earlier. They may be subtle or fragmentary and relatively easy to control pharmacologically. These infants show slow response to stimuli and their reaction may be incomplete. The infant usually lies in hypotonic position with abduction of arms and legs. A constant feature is the differential tone between upper and lower limbs. The arms show much less spontaneous movement and are relatively hypotonic compared with the legs **(Volpe, 2017).**Tendon jerks are exaggerated and Moro reflexes are incomplete. The suckling reflex is poor and feeding is incomplete. So, tube feeding is usually necessary. Autonomic nervous system dysfunction in the form of relative bradycardia and constricted pupils may occur **(Umar et al., 2018)**.

Shepherd et al. (2017) found that these infants show abnormal behavior for 4-7 days. If complete recovery occurs, it may take several weeks, but some improvement is usually seen by the end of the first week.

Severe HIE (grade III):

These infants are comatose and usually require respiratory support immediately after birth. There is severe hypotonia with no spontaneous movement, seizures are frequent and may be prolonged. The most severe asphyxiated infants of this group may have no seizure activity associated with isoelectric EEG. Tendon jerks and primitive reflexes are usually absent, pupils are fixed and dilated or react sluggishly to light **(Umar et al., 2018).**

Both moderate and severe HIE follow a progression of clinical signs by time as follows:

Birth to 12 hours:

The infants show signs of bilateral cerebral disturbances. The infants show depressed level of consciousness (usually deep stupor, or coma), respiratory disturbance (periodic breathing or respiratory failure), intact papillary and oculomotor responses, hypotonia and seizures by 6-12 hours in 50-60% of infants **(Volpe, 2017).**

From 12 to 24 hours:

The infant level of consciousness may appear to improve which is more apparent than real, because the appearance of alertness is not accompanied by the usual fixation responses to sensory stimuli or other signs of cerebral function **(Volpe, 2017).**

The infants show apparent increase in level of consciousness, more seizures, apneic spells, jitteriness and more weakness of upper limbs more than lower limbs in full term and lower limbs more than upper limbs in preterm **(Volpe, 2017).**

From 24 to 72 hours:

In severe HIE infants, level of consciousness often deteriorates and the infants develop deep stupor and coma. The infants show brainstem dysfunction in the form of deviation of the eye, loss of eye movement to doll's maneuver and papillary disturbances. They may show catastrophic deterioration with intraventricular hemorrhage in premature, respiratory arrest or even breathing irregularity may occur **(Volpe, 2017).**

After 72 hours:

The infants, who survive up this time, usually improve over the next several days to weeks but certain neurological features may persist. Although the level of consciousness improves, mild to moderate stupor continues. The persistence of impaired level of consciousness may require different diagnostic procedures to determine if it is associated with any complicating problems e.g. sepsis. The pattern of weakness and generalized hypotonia which occurs in the previous periods becomes more readily elicited. The rate of improvement of these clinical features is variable and not easily predicted. The infants who show rapid improvement will have the best term outcome. Infants with normal neurological examination by the end of the first week will have normal outcome **(Volpe, 2017).**

Miller system:

Boehme et al. (2014) validated a simple scoring system based on the typical signs and symptoms of Neonatal Encephalopathy (NE). The maximum score from the first 3 days of life is used for prognostication. In their study, no scoring was done when the subjects were sedated or paralyzed.

Clinical features of asphyxia

Perinatal asphyxia is that occurring in the period of 20 weeks of gestation through 28 days after birth **(Herrera and Silver, 2016).**

Target organs:

Table (4): Miller scoring system (encephalopathy system)

Variable	Score = 0	Score = 1
Feeding	Normal	Gavage, gastrostomy tube, or does not tolerate oral feeding
Alertness	Alert	Irritable, poorly responsive, or comatose
Muscle tone	Normal	Hypotonia or hypertonia
Respiratory status	Normal	Respiratory distress (need for continuous positive airway pressure or mechanical ventilation)
Reflexes	Normal	Hyperreflexia, hyporeflexia, or absent reflexes
Seizure	None	Suspected or confirmed clinical seizure

Target organs of perinatal asphyxia are the brain, heart, lung, kidneys, liver, bowel, and bone marrow. In a study of asphyxiated newborns, 34% had no evidence of organ injury, 23% had an abnormality confined to one organ, 34% involved two organs, and 9% had three affected organs. The most frequent abnormalities involved the kidney (50%), followed by CNS (28%), cardiovascular system (25%), and pulmonary system (23**%) (Rainaldi and Perlman, 2016).**

Diagnosis of perinatal asphyxia

Seven clinical features are used as possible markers of the condition and give some support to the diagnosis. These features are:

1. Fetal distress.

2. Passage of meconium.
3. Metabolic acidosis.
4. Failure to establish spontaneous respiration.
5. Depression of Apgar scores.
6. Hypoxic ischemic encephalopathy.
7. Multiorgan involvement.

The more the features are present, the more confident the diagnosis can be. The presence of fetal distress [Cardiotocogram (CTG) abnormality, passage of meconium or fetal acidosis], together with HIE, are absolute criteria for the diagnosis, and the others are supportive **(Herrera and Silver, 2016).**

A. **Antepartum assessment**:

The major means of antepartum assessment of human fetus include:

1- **Fetal movement**: Detected by maternal perception or by real-time ultrasonography **(Herrera and Silver, 2016)**.

2- **Fetal heart rate**: Non-Stress Test (NST) is response of fetal heart rate to movement. Contraction stress test is response of fetal heart rate to stimulation (oxytocin and nipple stimulation) or spontaneous uterine contraction **(Herrera and Silver, 2016).**

3- **Fetal biophysical profile**: It is a method of fetal assessment that combines the NST with variety of parameters determined by real-time ultrasound examination.

A score of 0 or 2 is assigned for the absence or presence of each of the following: fetal breathing, movement, tone, heart rate reactivity and amniotic fluid volume **(Herrera and Silver, 2016)**.

Reassuring test (8 to 10) are repeated weekly, less reassuring result (4 to 6) should be repeated later in the same day, scores 0 to 2 generally requires prompt delivery as the likelihood that a fetus will die in utero within one week **(O'Sullivan et al., 2018).**

4- **Fetal growth:** Detection of intrauterine growth retardation **(Looney et al., 2018).**

5- **Fetal blood flow velocity**: Detection by Doppler technique of flow velocity in umbilical and fetal systemic and cerebral vessels **(Herrera and Silver, 2016).**

B. Intrapartum assessment:

The major means of intrapartum assessment of the fetus include:

1- Meconium passage.

2- Fetal heart rate.

3- Fetal acid-base status.

4- Other techniques:

- Transcutaneous monitoring of blood gases and pH.
- Near-infrared spectroscopy.
- Doppler measurements of fetal blood velocity.
- Fetal electroencephalogram.

(Herrera and Silver, 2016)

C. Postnatal diagnosis

1- Depression of Apgar scores:

It is used to assess the state of newborn during the first critical minutes of life using five physiological signs (heart rate, respiratory effort, reflex irritability, muscle tone and color) **(Kliegman et al., 2016).**

Table (7): Apgar scoring system

Sign	**0**	**1**	**2**
Heart rate	Absent	<100 beats/minute	>100 beats/minute
Respiratory rate	Absent	Slow (irregular)	Good crying
Muscle tone	Limp	Some flexion of extremities	Active motion
Reflex irritability	No	Grimace	Cough or sneeze
Color	Blue, black	Pink body, blue, pale extremities	All pink

(Kliegman et al., 2016)

A total score of 10 indicates an infant in the best possible condition. An Apgar score 0-3 beyond 5 minutes is one suggestive criterion for intrapartum asphyxia insult but alone does not predict later neurologic dysfunction **(Killion, 2016).**

Table (8): Interpretation of Apgar score

Cumulative score after one or five minutes	**Interpretation**
7-10	No asphyxia
4-6	Moderate asphyxia
< 4	Sever asphyxia

(Volpe, 2017)

One minute Apgar score correlates with umbilical cord blood pH and is an index of intrapartum depression. However, Apgar scores beyond one minute are reflective of the infant's changing condition and the adequacy of resuscitative efforts, persistence of low Apgar scores indicates need for further therapeutic efforts **(Gomella et al., 2016).**

2- **Clinical manifestations**:

Within minutes of the onset of total fetal hypoxia, bradycardia, hypotension, decreased cardiac output, and severe metabolic as well as respiratory acidosis occur. The initial circulatory response of a fetus is increased shunting through the ductus venosus, ductus arteriosus, and foramen ovale, with transient maintenance of perfusion of the brain, heart and adrenals in preference to the lung, liver, kidneys and intestine **(Romero et al., 2017).**

As early as during labor and delivery, there may be indicators of perinatal asphyxia that in turn leads to HIE. They include changes in electronic fetal heart monitoring, acid-base abnormalities with umbilical cord blood pH less than 7, persistence of an Apgar score of 0 to 3 for greater than 5 minutes, and presence of meconium and placental pathology that may or ay not be evident on gross inspection. After birth, clinical manifestations are related to multiorgan involvement and include:

• Decreased level of consciousness, from delayed arousal to comatose state, absent or diminished developmental reflexes such as Moro, suckling, rooting, and palmar plantar grasps.

• Decreased tone, mostly axial, with head lag.

• Depressed deep tendon reflexes initially with exaggerated and pathological reflexes later on.

• Seizures.

• Decreased respiratory function and need for ventilatory support.

• Depression of cardiovascular functions and need for vasopressors.

• Manifestations from other organs such as liver, kidneys, adrenals, gastrointestinal system and bone marrow.

(Romero et al., 2017)

The occurrence of manifestations from other organ can at times assist a clinician in estimating the time of the insult. The presence of renal involvement, for example, with elevated BUN and creatinine but without hematuria at birth suggests that hypoxic-ischemic brain damage occurred 2 or more days before birth. The response of bone marrow to hypoxic-ischemic injury manifests as an increase in lymphocyte count above 10,000/mm^3 and a rise in normoblast count above 2,000/mm^3 within 2 hours of brain damage; lymphocyte count returns to normal within 24 hours while normoblast count within 24-36 hours of brain damage **(LaRosa et al., 2017).**

Based on the early manifestations, HIE has been classified into three stages (table 9). Those are helpful in predicting the outcome. Seizures are the most common manifestation of brain injury in newborns with reported incidence of one to 3.5 per 1,000 live births **(Volpe, 2017).**

Typically, the first occurs at 12-24 hours post-delivery; if they occur within the first 6 hours, they are most likely of non-hypoxic origin or hypoxia occurred prepartum **(LaRosa et al., 2017).**

Neonatal seizures have different manifestations depending on the newborn's gestational age. For the most part, they are subtle in presentation and may include some motor activity that is not bilaterally synchronized and alternates between two sides and autonomic dysfunction such as apnea, oxygen desaturation, and increase in heart rate. Whenever seizures are suspected, ECG monitoring is the best tool to aid a clinician in making a proper differential diagnosis between seizures versus non-seizure activity **(LaRosa et al., 2017)**.

Table (9): Sarnat and Sarnat stage of hypoxic-ischemic encephalopathy

Stage	**Grade 1**	**Grade 2**	**Grade 3**
Level of consciousness	Hyperalert	Lethargic or obtunded	Stuporous
Neuromuscular	Uninhibited, overactive	Obtunded	Diminished or absent spontaneous movement
Muscle tone	Normal	Diminished, spontaneous movement	Flaccid
Posture	Mild distal flexion	Mild hypotonia	Intermittent decerebration
Stretch reflexes	Overactive	Strong distal flexion	Decreased or absent
Segmental myoclonus	Present or absent	Overactive present	Absent
Complex reflex	Normal	Suppressed	Absent
Suckling	Weak	Weak or absent	Absent
Moro	Strong; low threshold	Weak, incomplete, high threshold	Absent
Oculovestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Automatic function	Generalized sympathetic	Generalized parasympathetic	Both system depressed

Pupils	Mydriasis	Miosis	Variable, often unequal, poor light reflex
Respiration	Spontaneous	Apnea	Periodic apnea
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial and salivary secretion	Sparse	Profuse	Variable
Gastrointestinal motility	Normal or decreased	Increased, diarrhea	Variable
Seizures	None	Common, focal or multifocal	Uncommon (excluding deceleration)
Electroencephalogram findings	Normal (awake)	**Early:** Generalized low voltage continuous delta, theta **Later:** Periodic pattern (awake), seizures (focal, multifocal), 1.5 Hz spike and wave	**Early:** Periodic pattern with isopotential phases **Later:** Totally isopotential
Duration	< 24 hours	2-14 hours	Hours to weeks
Outcome	About 100% normal	80% normal symptoms more than 5-7 days	Severe deficit about 50% die reminder with severe sequelae

(Sarnat and Sarnat, 1976, Gomella et al., 2016)

Laboratory studies:

There are no specific tests to confirm or exclude a diagnosis of HIE because the diagnosis is based on the history, physical and neurological examinations, and laboratory evidence. Many of the tests are performed to assess the severity of brain injury and to monitor the functional status of systemic organs. As always, the results of the tests should be interpreted in conjunction with the clinical history and the findings from physical examination. Laboratory studies should include the following:

- **Serum electrolyte levels:**

- In severe cases, daily assessments of serum electrolytes are valuable until the infant's status improves. Markedly low serum sodium, potassium, and chloride levels in the presence of reduced urine flow and excessive weight gain may indicate acute tubular damage or **Syndrome of**

Inappropriate Antidiuretic Hormone (SIADH) secretion, particularly during the initial 2-3 days of life **(Mohd et al., 2011).**

- Similar changes may be seen during recovery; increased urine flow may indicate ongoing tubular damage and excessive sodium loss relative to water loss. **(Lespay-Rebolledo et al., 2018)**

• **Renal function studies**: Serum creatinine levels, creatinine clearance, and BUN levels suffice in most cases.

• **Cardiac and liver enzymes**: These values are an adjunct to assess the degree of hypoxic-ischemic injury to these organs. These findings may also provide some insight into injuries to other organs, such as the bowel.

• **Coagulation system evaluation**: This includes prothrombin time, partial thromboplastin time, and fibrinogen levels.

• **ABG:** Blood gas monitoring is used to assess acid-base status and to

avoid hyperoxia and hypoxia as well as hypercapnia and hypocapnia.

(Patel et al., 2017)

Radiological investigations:

• **Brain MRI:**

- MRI is the imaging modality of choice for the diagnosis and follow-up of infants with moderate-to-severe HIE. Conventional MRI sequences (T_1W and T_2W) provide information on the status of myelination and preexisting developmental defects of the brain. When performed after the first day (and particularly after day 4), conventional images may accurately demonstrate the injury pattern as area of hyperintensity. Conventional images are most helpful at age 7-10 days, when DWI findings have pseudonormalized.

- DWI allows earlier identification of injury patterns in the first 24-48 hours. The MRI sequence identifies areas of edema and, hence, injured areas. DWI changes peak at 3-5 day and pseudonormalizes by the end of the first week. In neonates, DWI changes may underestimate the extent of injury, most likely because of the importance of apoptosis in the ultimate extent of neurological injury.

- MRI is also a useful tool in the determination of prognosis. Infants with predominant injuries to the basal ganglia or thalamus have an unfavorable neurological outcome when compared with infants with a white matter predominant pattern of injury.

- MRI is also useful for follow-up. In any newly diagnosed case of cerebral palsy, MRI should be considered because it may help in establishing the cause.

(De Wispelaere et al., 2019)

- **Cranial ultrasonography***:* Although portable and convenient, cranial ultrasonography has a low sensitivity (50%) for the detection of anomalies associated with hypoxic-ischemic encephalopathy. Findings include global increase in cerebral echogenicity and obliteration of Cerebrospinal Fluid (CSF) containing spaces suggestive of cerebral edema. Increase in the echogenicity of deep gray matter structures may also be identified, typically when ultrasonography is performed after 7 days of life. Finally, head ultrasonography is helpful upon admission, particularly in patients evaluated for hypothermia therapy, to rule out intracerebral or intraventricular hemorrhages **(Barnette et al., 2014).**

- **Head CT scanning:**

- A CT scan of the head can be useful to confirm cerebral edema (obliteration of cerebral ventricles and blurring of sulci), manifested as narrowness of the lateral ventricles and flattening of gyri. Areas of reduced density that indicate evolving zones of infarction may be present.

- Evidence of hemorrhage in the ventricles or in the cerebral parenchyma may also be seen.

- However, evidence suggests that even a single CT scan exposes children to potentially harmful radiation. In view of this evidence, MRI has now largely supplanted head CT in the evaluation of neonates with hypoxic-ischemic encephalopathy.

(Groenendaal and de Vries, 2017)

- **.Echocardiography:** In infants requiring inotropic support, Echocardiography (ECHO) helps to define myocardial contractility and the existence of structural heart defects **(Mendes et al., 2017)**.

Other tests:

• Amplitude-integrated Electroencephalography (aEEG)

- Several studies have shown that a single-channel aEEG performed within a few hours of birth can help evaluate the severity of brain injury in the infant with hypoxic-ischemic encephalopathy.

- In addition, aEEG findings have been used as criteria for inclusion in the CoolCap trial of selective head cooling. However, some evidence argues against the use of aEEG as a tool to exclude infants with hypoxic-ischemic encephalopathy from receiving hypothermia therapy.

- Note that considerable training is required for conducting and properly interpreting the aEEG findings. **(De Wispelaere et al., 2019)**

- **Standard EEG**:

- Traditional, multichannel EEG is an integral part of the evaluation of infants diagnosed with hypoxic-ischemic encephalopathy. It is a valuable tool to assess the severity of the injury and evaluate for subclinical seizures. This is particularly important for infants on assisted ventilation requiring sedation or paralysis.

- Generalized depression of the background rhythm and voltage, with varying degrees of superimposed seizures, are early findings.

- Caution in interpreting early severe background abnormalities needs to be applied because reverting to normal background pattern in few days of life can be associated with normal outcomes. Note that large doses of anticonvulsant therapy may alter the EEG findings.

- Serial EEGs should be obtained to assess seizure control and evolution of background abnormalities. Early EEGs are important not only to evaluate the degree of encephalopathy and the presence of seizures but may also help establish early prognosis. Serial EEGs are also helpful in establishing prognosis. Improvement in the EEG findings over the first week, in conjunction with improvement in the clinical condition, may help predict a better long-term outcome. **(Jose et al., 2013)**

Treatment of hypoxic ischemic encephalopathy

Medical care:

Following initial resuscitation and stabilization, treatment of HIE is largely supportive and should focus on adequate ventilation and perfusion, careful fluid management, avoidance of hypoglycemia and hyperglycemia and treatment of seizures. Intervention strategies aim to avoid any further brain injury in these infants **(Yildiz et al., 2017)**.

Initial resuscitation and stabilization:

Delivery room management follows standard Neonatal Resuscitation Program (NRP) guidelines. Close attention should be paid to appropriate oxygen delivery, perfusion status, and avoidance of hypoglycemia and hyperthermia **(Fitzgerald et al., 2019).**

A lot of attention is currently focused on resuscitation with room air versus 100% oxygen in the delivery room. Several clinical trials indicate that room air resuscitation for infants with perinatal asphyxia is as effective as resuscitation with 100% oxygen. In addition, infants resuscitated with room air have a lower level of circulating markers of oxidative stress. However, studies indicating that time to return to spontaneous circulation is equivalent with room air resuscitation are lacking. Given these limitation, current International Liaison Committee on Resuscitation (ILCOR) recommendations include initiating neonatal resuscitation with concentrations of oxygen between 21-100%) **(Fitzgerald et al., 2019).**

Supportive care in patients with hypoxic-ischemic encephalopathy:

Most infants with severe hypoxic-ischemic encephalopathy need ventilatory support during first days of life. Although animal data suggest that permissive hypercapnia may be neuroprotective, no such evidence is available in newborn. Therefore, the role of mechanical ventilation is to maintain the blood gases and acid-base status in the physiological ranges and prevent hypoxia, hyperoxia, hypercapnia, and hypocapnia. Hypocapnia in particular may lead to severe brain hypoperfusion and cellular alkalosis and has been associated with worse neurodevelopmental outcomes. Infants with hypoxic-ischemic encephalopathy are also at risk for pulmonary hypertension and should be monitored. Nitric Oxide (NO) may be used according to published guidelines **(Yildiz et al., 2017).**

Perfusion and blood pressure management:

Studies indicate that a mean Blood Pressure (BP) above 35-40 mm Hg is necessary to avoid decreased cerebral perfusion. Hypotension is common in infants with severe hypoxic-ischemic encephalopathy and is due to myocardial dysfunction, capillary leak syndrome, and hypovolemia; hypotension should be promptly treated. Dopamine or dobutamine can be used to achieve adequate cardiac output in these patients. Avoiding iatrogenic hypertensive episodes is also important **(Schump, 2018).**

Fluid and electrolyte management:

Because of the concern for Acute Tubular Necrosis (ATN) and Syndrome of Inappropriate Antidiuretic Hormone (SIADH) secretion, fluid restriction is typically recommended for these infants until renal function and urine output can be evaluated. However, this recommendation is not based on evidence from randomized controlled trials. Therefore, fluid and electrolyte management must be individualized on the basis of clinical course, changes in weight, urine output, and the results of serum electrolyte and renal function studies **(Simiyu et al., 2017).**

The role of prophylactic theophylline, given early after birth, in reducing renal dysfunction after hypoxic-ischemic encephalopathy has been evaluated in 3 small randomized controlled trials. In these studies, a single dose of theophylline (5-8 mg/kg) given within one hour of birth resulted in:

(1) Decreased severe renal dysfunction (defined as creatinine level > 1.5 mg/dl for 2 consecutive days);

(2) Increased creatine clearance;

(3) Increased Glomerular Filtration Rate (GFR); and

(4) Decreased b_2 microglobulin excretion.

(Widziszowska and Namyslowski, 2011)

Fluid and glucose homeostasis should be achieved. Avoid hypoglycemia and hyperglycemia because both may accentuate brain damage. Hypoglycemia in particular should be avoided. In a retrospective study, Salhab et al showed that initial hypoglycemia (< 40 mg/dl) is significantly associated with adverse neurological outcome **(Lespay-Rebolledo et al., 2018).**

Treatment of seizures:

Hypoxic-ischemic encephalopathy is the most common cause of seizures in the neonatal period. Seizures are generally self-limited to the first days of life but may significantly compromise other body functions, such as maintenance of ventilation, oxygenation, and blood pressure. Additionally, studies suggest that seizures, including asymptomatic electrographic seizures, may contribute to brain injury and increase the risk of subsequent epilepsy **(Chen et al., 2017).**

Hypothermia protocol:

Cooling must be initiated within 6 hours of birth as research has demonstrated this period as an optimal time for hypothermia to decrease the extent of the brain injury. Thus, the NICU must be prepared and well organized given the time constraint. The first step is to screen the infant for eligibility before accepting him for the therapy. When the infant meets the criteria, the equipment is quickly assembled to the bedside and the blanket is precooled, but hung behind the radiant warmer. Because a thorough physical and neurological examination is required to determine eligibility for the protocol, the infant is admitted to a prewarmed radiant warmer on servo control. In addition to an amplified EEG, head ultrasound, and an echocardiogram, the physician will note the infant's level of consciousness, posture, tone, presence of any spontaneous activity, and quality of primitive reflexes (suckling and Moro) and evaluate the autonomic nervous system (quality of respiration, heart rate, and pupils) **(Sebetseba et al., 2017).**

Immediately after establishing eligibility, the infant is placed on the precooled blanket with one regular hospital baby blanket under him. An esophageal temperature probe is inserted through a nare to a level of T_{6-9}, which corresponds to approximately 2 cm above the diaphragm. Placement is confirmed radiographically. The esophageal temperature probe is connected to the temperature cable and the radiant warmer is turned to manual control with the heater in the off position **(Martinello et al., 2017).**

Follow-up:

Close physical therapy and developmental evaluations are needed prior to discharge in patients with HIE. The goal of follow-up is to detect impairments and promote early intervention for those infants who require it:

• Growth parameters including head circumference should be closely monitored in all infants with hypoxic-ischemic encephalopathy.

• In infants diagnosed with moderate-to-severe hypoxic-ischemic encephalopathy with either abnormal neurologic examination findings or feeding difficulties, intensive follow-up is recommended. This should include follow-up by developmental pediatrician and pediatric neurologist. Evaluation by a pediatric ophthalmologist is also recommended for these infants because damage to the posterovisual cortex can occur. Hearing testing should occur prior to discharge from the NICU and may need to be repeated in infants at risk for late-onset hearing loss (e.g. pulmonary hypertension and antibiotic use).

• In infants with moderate hypoxic-ischemic encephalopathy but no feeding difficulties and normal neurologic examination findings, routine care is appropriate. If hypothermia therapy was used in the neonatal period, follow-up is recommended for the continued evaluation of the efficacy and safety of this newly introduced therapy. Data should be entered into the available registries, databases, or both whenever possible.

• Infants with mild hypoxic-ischemic encephalopathy generally do well and do not require specialized follow-up.

(Liu et al., 2017)

Prognosis:

Accurate prediction of the severity of long-term complications is difficult, although clinical, laboratory, and imaging criteria have been used. The following criteria have been shown to be the most helpful in outlining likely outcomes:

• Lack of spontaneous respiratory effort within 20-30 minutes of birth is almost always associated with death.

• The presence of seizures is an ominous sign. The risk of poor neurological outcome is distinctly greater in such infants, particularly if seizures occur frequently and are difficult to control.

• Abnormal clinical neurological findings persisting beyond the first 7-10 days of life usually indicate poor prognosis. Among these, abnormalities of muscle tone and posture (hypotonia, rigidity and weakness) should be carefully noted.

• EEG at about 7 days that reveals normal background activity is a good prognostic sign.

• Persistent feeding difficulties, which generally are due to abnormal tone of the muscles of suckling and swallowing, also suggest significant CNS damage.

• Poor head growth during the postnatal period and the first year of life is a sensitive finding predicting higher frequency of neurologic deficits.

• Of note, the use of hypothermia therapy changes the prognostic value of clinical evaluation in infants with hypoxic-ischemic encephalopathy and its impact on predicting outcomes is still under evaluation. **(Bano et al., 2017)**

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