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Review Article

PERINATAL ASPHYXIA AND HYPOXIC-ISCHAEMIC ENCEPHALOPATHY (HIE)

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ABSTRACT

Perinatal asphyxia is a common and serious neonatal problem globally and it significantly contributes to both neonatal morbidity and mortality. It is the fifth largest cause of under-five mortality. Despite the important advances in perinatal care in the past decades, asphyxia remains a severe condition leading to significant mortality and morbidity. Many preconceptional, antepartum and intrapartum risk factors have been shown to be associated with perinatal asphyxia. Asphyxial injury may involve virtually every organ system of the body, but hypoxic-ischemic encephalopathy (HIE) is the most studied clinical condition and that exhibiting the most serious sequelae. Neonates with suspected HIE are classified according to the Sarnat staging system, which divides neonates into mild, moderate, or severe categories, and measures the progression of the neurologic insult to predict a neonate's prognosis. A clinical evaluation, blood gas analysis, laboratory examinations as well as various neuroimaging techniques are required in order to assess and manage the asphyxiated newborns and HIE. Currently, several biomarkers are available and may help clinicians to globally assess newborns with hypoxic-ischemic injury. Management of birth asphyxia includes supportive care with emphasis on vital care, respiratory and cardiovascular support, maintenance of normo-glycemia and normo-thermia and seizures management whereas, in HIE, therapeutic hypothermia and systemic supportive care form the cornerstone of therapy.

The objective of this paper is to provide a current overview on the perinatal asphyxia and hypoxic-ischemic encephalopathy (HIE), to evaluate the risk factors, pathophysiology, diagnostic considerations and the treatment.

Keywords: Perinatal asphyxia; Hypoxic-ischaemic encephalopathy; Newborns; Apgar score; Risk factors.

INTRODUCTION

The term “asphyxia” is derived from the Greek and means “stopping of the pulse”. Asphyxia is defined as the inability of the newborn to initiate and sustain adequate respiration after delivery [1] . Birth asphyxia also termed perinatal asphyxia is an obstetric complication that strongly affects brain structure and function. Perinatal asphyxia and birth asphyxia are synonymous: both refer to the period not only immediately before birth and throughout labor, but also birth itself and the immediate postpartum period, generally thought of as the period of stabilization right after birth. The American College of Obstetricians and Gynecologists and the American Academy of Pediatrics assign a neonate to be asphyxiated if the following conditions are fulfilled: Umbilical cord arterial pH <7; Apgar score of 0-3 for longer than 5 min; neurological manifestations (e.g., seizures, coma, or hypotonia); and multisystem organ dysfunction, e.g., cardiovascular, gastrointestinal, hematological, pulmonary or renal system [2].

Birth asphyxia is one of the principal causes of early neonatal death. In survivors it may evolve to hypoxic-ischaemic encephalopathy and major long-term neurological morbidity. Prolonged and intense asphyxia will lead to energy exhaustion in tissues exclusively dependent on aerobic metabolism, such as the central nervous system. Perinatal asphyxia may affect virtually any organ, but hypoxic-ischemic encephalopathy (HIE) is the most studied clinical condition and that is burdened with the most severe sequelae. Estimates of the incidence of perinatal asphyxia are quite variable from one study to another. De Haan et al. [3] reported an incidence of perinatal asphyxia of 1 to 6 per 1,000 live full-term births. Moreover, asphyxia has been shown to be the third most common cause of neonatal death (23%) after preterm birth (28%) and severe infections (26%) [4]. Robertson et al. [5] define HIE as “an acute non-static encephalopathy caused by intrapartum or late antepartum brain hypoxia and ischemia”. This clinical condition evolves during the first days of life after significant hypoxic-ischemic insult, and is a leading predictor of neurodevelopmental disability [6]. Sarnat and Sarnat [7] classified HIE into 3 clinical stages: mild (stage 1), moderate (stage 2) and severe (stage 3) encephalopathy. The incidence of HIE ranges from 1 to 8 per 1000 live births in developed countries and is as high as 26 per 1000 live births in underdeveloped countries [8].

Risk factors of perinatal asphyxia:

In term newborns, asphyxia can occur in utero and during labor and delivery as a result of impaired placental gas exchange. Preconceptional risk factors for asphyxia are maternal age ≥ 35 years, social factors, family history of seizures or neurologic disease, infertility treatment, previous neonatal death etc. Antepartum risk factors include maternal prothrombotic disorders and proinflammatory states, maternal thyroid disease, severe preeclampsia, multiple gestation, chromosomal/genetic abnormalities, congenital malformations, intrauterine growth restriction, trauma, breech presentation and antepartum hemorrhage. Numerous intrapartum risk factors for asphyxia are recognized, including abnormal fetal heart rate during

labor, chorioamnionitis/maternal fever, thick meconium, operative vaginal delivery, general anesthesia, emergency cesarean delivery, placental abruption, umbilical cord prolapse, uterine rupture, maternal cardiac arrest, and fetal exsanguination. Asphyxia can also occur in the immediate postnatal period, usually secondary to pulmonary, neurological or cardiovascular abnormalities. It should be noted that, in many cases, the timing of asphyxia cannot be established with certainty. Drugs such as morphine, pethidine and anaesthetic agents depress the respiratory centres directly and the chance of development of asphyxia is increased. The prognosis and severity of the symptoms of child with birth asphyxia depend on the risk factors and management of the patient.

Pathophysiology of birth asphyxia and HIE:

The process leading to birth asphyxia is heterogeneous and has many causal pathways starting either pre-conceptionally or in the antepartum period. It may occur in utero, during labour and delivery, or in the immediate postnatal period as a result of multiple causes, that include placental abruption, cord compression, trans-placental anaesthetics, narcotic administration, intrauterine pneumonia, severe meconium aspiration, congenital cardiac or pulmonary anomalies, and birth trauma. Postnatal asphyxia can be caused by an obstructed airway, maternal opiates consumption or administration that can cause respiratory depression.

Failure to initiate breathing at birth leads to hypoxic ischemic injury to the brain resulting in clinical manifestations termed as hypoxic ischemic encephalopathy (HIE). As soon as an asphyxial event occurs, compensatory mechanisms are initiated with the fetus responding to redistribute and maintain perfusion to vital organs of the body. In adults cerebral blood flow is auto-regulated over a wide range of mean systemic blood pressure of 40 mm Hg whereas in newborns this range is not more than 10-20 mm Hg, making maintenance of cerebral blood flow very challenging. When cerebral auto-regulatory mechanism fails, cerebral blood flow becomes dependent on systemic blood pressure that is already compromised by the asphyxial insult. This leads to cerebral ischemia causing neuronal cell hypoxia and primary intracellular energy failure, further resulting in dropping brain temperature along with release of inhibitory neurotransmitters like GABA (Gamma Amino Butyric Acid) as body's protective mechanism attempts to decrease oxygen demand of neuronal cells in order to minimize the effects of hypoxia [9]. This period of primary energy failure and early cell death (mainly by necrosis and a small degree of apoptosis) lasts around 6 hours but may extend up to 24 hours of age providing a window of opportunity for therapeutic interventions. If the above process is not intervened with, secondary energy failure and reperfusion injury ensues. This is believed to be due to oxygen free radical production, intracellular calcium entry into the cells (gating mechanism) leading to increased levels of neuronal cell death by apoptosis, culminating in long term neurodevelopmental consequences[9].

The consequences of hypoxic-ischemic insult usually extend to other organ systems in addition to the

brain. In a minority of cases (< 15%), the brain is the only organ that exhibits dysfunction after asphyxia. In most cases, systemic hypoxia-ischemia results in multiorgan dysfunction. The lungs of asphyxiated newborns can be injured by hypoxia, as a result of inhaled meconium, secondary to cardiac dysfunction, or compromised due to pulmonary hypertension [10]. Accordingly, gas exchange is impaired and assisted ventilation may be needed. Hypoxia-ischemia causes a direct damage to the myocardium. Myocardial ischemia compromises cardiac conduction and contractile efficiency, often requiring an inotropic support to maintain adequate circulation. Functional and conduction abnormalities may be detected by echocardiography and electrocardiogram, while heart muscle damage is reflected by the increase of cardiac enzymes.

The other multisystem effects regard kidneys, liver, and bone marrow. Kidney injury represents the best systemic marker of brain injury. Oligo-anuria following hypoxic-ischemic injury is common, frequently associated with hematuria, and results from renal tubular damage. Serum creatinine and blood urea concentrations increase progressively, reaching the peak in the days following the injury. Fluid retention and hyponatremia may occur due to inappropriate secretion of antidiuretic hormone.

The effects on the bone marrow include an increased release of nucleated red blood cells (NRBC) and thrombocytopenia. The NRBC count reaches a peak at 6-8 hours following brain injury and returns to normal by 36-72 hours. On the other hand, the platelet count falls sometimes by 12 hours, and reaches the nadir at 2-3 days. Thrombocytopenia can be severe enough to determine or aggravate bleeding (risk of intracerebral bleeding). Liver dysfunction may be manifested by increased hepatocellular enzymes, even though more extensive damage may develop.

Fluctuations of blood glucose concentration may be observed, with hypoglycemia being most common. Hypoglycemia may result in neurological sequelae, particularly when it causes or accompanies seizures. On the other hand, hyperglycemia may also lead to, or aggravate, brain damage through a mechanism involving a hyperosmolar state [11].

Clinical conditions aggravating hypoxic-ischemic brain injury:

There is evidence that a number of common clinical events including hypoglycemia, hyperthermia and seizures may aggravate the hypoxic-ischemic brain injury; therefore, particular attention should be paid to the prevention and treatment of them to avoid additional injury. The administration of oxygen during resuscitation after asphyxia may also contribute to hypoxic-ischemic brain injury. In fact, hyperoxia resulting from the use of high concentrations of oxygen can lead to an excessive release of free oxygen radicals, thus aggravating brain injury. Accordingly, oxygen delivery during neonatal resuscitation should be carefully controlled, and oxygen saturation monitored, in order to avoid hyperoxia.

Diagnostic Considerations:

A clinical evaluation and laboratory examinations are required in order to assess and manage the asphyxiated newborn. The American College of Obstetricians and Gynecologists and the American Academy of Pediatrics assign a neonate to be asphyxiated if the following conditionsare fulfilled: Umbilical cord arterial pH <7; Apgar score of 0-3 for longer than 5 min; neurological manifestations (e.g., seizures, coma, or hypotonia); and multisystem organ dysfunction, e.g., cardiovascular, gastrointestinal, hematological, pulmonary or renal system.

Whilst the above criteria may be useful and applicable in developed countries, they cannot be practically made use of in a resource limited country where the local traditional birth attendants have little knowledge of APGAR scoring and even in many hospitals availability of umbilical blood gases remains a luxury. Taking a pragmatic view we would recommend adopting a modified WHO definition of birth asphyxia i.e. any baby who fails to initiate and sustain breathing at birth should be considered to be suffering from asphyxia until and unless proven otherwise.

Neonates with suspected HIE are classified according to the Sarnat staging system,[7] which evaluates the level of consciousness, muscletone, tendon reflexes, complex reflexes, and autonomic function. The Sarnat stage classifies neonatal HIE into the following 3 categories: stage I (mild), stage II (moderate), and stage III (severe).

	Mild HIE (I)	Moderate HIE (II)	Severe HIE (III)
Level of consciousness	Hyperalert	Lethargic	Stuporose
Muscle tone	Normal	Mild hypotonia	Flaccid
Complex reflexes			
Suck	Normal/Weak	Weak/Absent	Absent
Moro	Strong	Weak/Incomplete	Absent
Seizures	Absent	Common	Frequent/difficult to control

Table 1: Hypoxic-ischemic encephalopathy (HIE). Classification modified from Sarnat and Sarnat (1976)

Blood gas analysis:

The blood gas criteria that define perinatal asphyxia causing brain injury are uncertain. Nevertheless, the pH and base deficit on the umbilical cord or first blood gas is useful for determining which newborns have asphyxia requiring further evaluation for the development of HIE. The best indicator for intrapartum

asphyxia is severe metabolic acidosis (pH < 7.0 and base deficit ≥ 12 mmol/L) in umbilical cord arterial blood at delivery.

Neuroimaging:

Cranial and Doppler ultrasonography, computerized tomography (CT) and magnetic resonance imaging (MRI) are the most commonly used brain imaging techniques.

Cranial ultrasonography (CS) has been used widely in neonatal practice, as it is a convenient, non-invasive, safe and quick imaging technique to visualize the neonatal brain parenchyma and ventricular system serially without disturbing or moving the patient. Sequential cranial ultrasound examinations following a recent hypoxic-ischemic insult are helpful for assessing the evolution of injury, and particularly for defining the pattern of lesions and the timing of their onset. Nevertheless, CS does not allow early identification of asphyxial brain injury that becomes evident between 24 and 72 hours after birth [12].

Doppler ultrasonography (DS) completes the CS exam, providing important information about two parameters, the resistive index (RI) and the end-diastolic flow velocity (EDFV). Reduced RI and increased EDFV values have been revealed in the anterior cerebral artery in case of neonatal asphyxia; they seem to indicate an alteration in the cerebral blood flow due to the vasodilation resulting from hypercapnia or metabolites accumulation.

Computerized tomography has been used in the past in term infants with HIE. Magnetic resonance imaging (MRI) has been shown to be superior to CT in all aspects. MRI is the optimum imaging modality for the early assessment of brain injury in asphyxiated term neonates. Compared with CS and CT, MRI can visualize cerebral hypoxic-ischemic lesions with higher resolution, sensitivity and specificity. It is able to detect 75-100% of cerebral lesions resulting from asphyxia, particularly those affecting white-matter, basal ganglia and thalamus [13]. MRI has the advantage of not exposing the newborn to ionizing radiation. Brain MRI is the preferred imaging choice in neonates with HIE and is a useful tool to predict long-term outcomes. Abnormalities in the MRI of the brain correlate with outcomes. Lower apparent diffusion coefficient values in the basal ganglia during the first 7days after HIE predict adverse neurologic outcomes [14]. Injuries to the posterior limb of the internal capsule and basal ganglia are associated with motor deficits [15]. Injury to the posterior limb of the internal capsule combined with diffuse basal ganglia injury and a peripheral (ie, hemispheric gray and white matter) abnormality are associated with death, hearing and visual impairments, and severe cerebral palsy [16]. Advanced MRI techniques, including MR spectroscopic imaging (MRSI) and diffusion tensor imaging (DTI), can more accurately identify brain injury in an earlier stage.

Electroencephalography and cerebral function monitoring:

Different tools are available to study electric function of the neonatal brain, in particular standard

electroencephalography (EEG) and cerebral function monitoring (CFM). A recent study has evaluated the relation between EEG patterns and neurological outcomes in term newborns with HIE, showing that a normal EEG is correlated with a normal outcome, whereas the presence of "burst suppression" on EEG is predictive of death or pathological outcome [17]. Sequential EEG, in newborns with seizures, has been found to have more predictive value to estimate the neurological outcome and postnatal death, as compared to a single EEG recording.

The CFM is a real-time monitoring device that uses a method known as amplitude-integrated EEG (aEEG). CFM is commonly used for bedside monitoring of background neurological activity in term and near-term infants with encephalopathy. CFM patterns are well correlated with those obtained with regular EEG, even though short or low amplitude seizures cannot be detected with CFM. Therefore, CFM should never replace regular EEG, and a standard EEG is always recommended in newborns with HIE. CFM has been shown to be useful to assess asphyxiated newborns in combination with neurologic examination, and to select and manage those infants requiring particular treatments such as hypothermia.

Laboratory evaluation:

Neonatal asphyxia is often followed by a multiorgan failure involving mainly the kidney, brain, and heart. Multiorgan failure is associated with poor prognosis and high mortality. Currently, several biomarkers are available and may help clinicians to globally assess newborns with hypoxic-ischemic injury.

Markers of kidney damage:

Kidney is one of the most important organs commonly involved in the multiple organ dysfunction caused by perinatal asphyxia. The severity of renal damage ranges from mild disorders to acute kidney failure. Evaluations of blood urea and serum creatinine levels are the tests most frequently used to assess renal injury caused by perinatal asphyxia. Currently, these indicators are not considered helpful to the early identification of renal damage. In fact, they reflect the glomerular damage, and the consequent reduction of glomerular filtration rate (GFR), that occurs at least 24 hours after the hypoxic insult and when about 50% of nephrons are compromised. Asphyxial insult causes an earlier and subtler damage of tubular cells, determining their necrosis. Accordingly, markers of tubular dysfunction such as urinary β2 microglobulin have been found to be better indicators of early renal injury. Furthermore, a recent study highlighted that the increase of urinary β2 microglobulin is directly related both to asphyxia grading (Apgar score) and to Sarnat and Sarnat staging of HIE [18]. Cystatin C is another marker of renal damage. This protein, produced by all nucleated cells, is filtered by the glomeruli and degraded by proximal tubular cells. It does not cross the placental barrier and is not influenced by any newborn conditions. Recently, cystatin C level has been shown to be a good indicator of GFR; it is able to identify even mild forms of glomerular dysfunction, and decreases

in newborns with perinatal asphyxia [19].

Markers of central nervous system damage:

The availability of markers of neurological damage may be very important to target therapy, evaluate response to treatment, and predict neurodevelopmental outcomes. Hypoxia, both acute and chronic, is a well-known cause of an increased count of nucleated red blood cells (NRBC). A recent study has been conducted to evaluate the power of this parameter in predicting neurological outcomes in asphyxiated newborns. Both NRBC count and NRBC count per 100 white blood cells (NRBC/100WBCs) have been found to be higher in those patients that exhibited a convulsion in the first 12 hours after birth, and in those patients that subsequently developed HIE stage III. The newborns that died or those with sequelae had a significantly higher NRBC count [20]. Glial fibrillary acid protein (GFAP) and ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1), normally expressed either in neurons and in astrocytes, are easily measurable markers of neuronal apoptosis as they are released into blood circulation after a blood-brain barrier damage caused by hypoxia. A pilot study found that UCH-L1 and GFAP levels were associated with the worst outcomes in newborns with HIE, being increased in those patients that died or in those with severe brain injury at MRI [21]. Another biomarker of CNS damage is S-100β protein. It is mainly synthesized by astroglial cells and increases in the blood after their death and when the blood-brain barrier is damaged. This marker was documented to be increased in the first urine of newborns with HIE and to be a good predictor of neonatal death when its value is higher than 1 mcg/l [22]. S-100β level has been studied also in blood samples, documenting that it correlates with the development of severe or moderate forms of HIE. Finally, serum S-100β protein was found to increase very early after asphyxial insult, from about 2 hours after birth [23]. Brain-derived neurotrophic factor, a neurotrophin that normally fosters brain cell growth and differentiation, has been shown to have higher levels in newborns with HIE compared with normal newborns. The interleukin-6, a biomarker non specific for brain damage, was found to be related with both severity of HIE and neurological outcomes at 2 years after birth. Creatine kinase BB (CK-BB), normally contained in astrocytes and neurons, can be found in serum after neonatal asphyxia. Nagdyman et al. [23] observed that serum concentration of CK-BB was an early predictor of HIE as its rise occurred from 2 hours after birth.

However, the study suggests that no single biomarker is able to assess neurological damage after perinatal asphyxia; a panel of multiple biomarkers should probably be considered in evaluating the clinical consequences of asphyxia, and in initiating, continuing or stopping neuroprotective therapy.

Markers of cardiac damage:

ECG and cardiac enzymes measurement are used to assess myocardial dysfunction. Serum level of Cardiac troponin I (cTnI) at 72 hours after birth appears to be a significant predictor of mortality in term newborns with HIE [24]. Furthermore, Agrawal et al. [25] have shown that mean creatine kinase total levels,

creatine kinase-myocardial band (CK-MB) and cTnI values rise proportionally with the severity of HIE. In asphyxiated newborns, ECG monitoring and enzyme measurement appear to be useful to evaluate cardiac function and establish an adequate treatment.

TREATMENT

The treatment of asphyxia starts with a correct perinatal management of high-risk pregnancies. The management of the hypoxic-ischemic newborns in the delivery room is the second fundamental step of the treatment. The initial management of asphyxiated newborns following admission to the neonatal intensive care unit (NICU) does not target the pathophysiologic sequence resulting in hypoxic-ischemic brain injury, but rather is aimed at avoiding injury resulting from secondary events related to hypoxia-ischemia. An early identification and treatment of the most common events that could aggravate brain damage and a good and early supportive intensive care have been shown to be essential to avoid or to reduce the ongoing brain injury in asphyxiated newborns. Temperature control, respiratory and cardiac support, seizures treatment, maintaining normal blood glucose, hematocrit, and electrolytes values, correcting blood gases and acid-base status alterations are a must in the management of this category of newborns [26].

Hypothermia and systemic supportive care form the cornerstone of therapy for HIE. Therapeutic hypothermia is considered the standard of care for neonates with HIE; the treatment uses mild hypothermia in the range of 33.5°C to 35.0°C. Several large multicenter trials demonstrated that the therapy is safe and efficacious [27]. Therapeutic hypothermia reduced the risk for death or major neurodevelopmental disabilities at 18 months of age in neonates with moderate and severe HIE [27].

Many promising neuroprotective agents might contribute to reduce hypoxic-ischemic brain injury through different mechanisms of action, but further studies are required to confirm their efficacy. The most studied neuroprotective pharmacological agents are allopurinol, deferoxamine, topiramate, xenon , melatonin [28], erythropoietin and magnesium; they might contribute to reduce brain injury through different mechanisms of action. These agents appear to be beneficial when administered alone or in combination with hypothermia, but further studies are required to confirm their neuroprotective efficacy.

Perinatal asphyxia is burdened with high morbidity and mortality. Reported mortality rate is about 20% in full-term asphyxiated infants, while the incidence of neurological impairments in survivors is estimated to be of about 25% [29,30]. Nevertheless, there is a large variety of literature data regarding mortality and neurological outcome rates.The study by Graham et al. [31] has shown that HIE results in cerebral palsy in at least 14% of cases.

CONCLUSIONS

Perinatal asphyxia also termed birth asphyxia is a common and serious neonatal problem globally

and it significantly contributes to both neonatal morbidity and mortality. Perinatal asphyxia may affect virtually any organ, but hypoxic-ischemic encephalopathy (HIE) is the most studied clinical condition and that is burdened with the most severe sequelae. The process leading to birth asphyxia is heterogeneous and has many causal pathways starting either pre-conceptionally or in the antepartum period. It may occur in utero, during labour and delivery, or in the immediate postnatal period. A clinical evaluation, blood gas analysis, laboratory examinations as well as various neuroimaging techniques are required in order to assess and manage the asphyxiated newborns and HIE. Management of birth asphyxia is mainly supportive with emphasis on vital care, respiratory and cardiovascular support, maintenance of normo-glycemia and normo-thermia and management of seizures whereas, in HIE, Hypothermia and systemic supportive care form the cornerstone of therapy. According to different studies,therapeutic hypothermia is considered the standard of care for neonates with HIE.

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