Introduction

Pediatricians and family practitioners have less experience with the advances in NICU care than they did 2-3 decades ago. Limited time to spend in the follow-up care of NICU graduates. The evaluation of preterm and term infants with complex conditions requires the involvement of professionals from multiple medical, rehabilitative, psychological, and social-service subspecialties ***(Saigal and Doyle, 2008).***

The primary goals of perinatal care are to decrease infant mortality, enhance health-related quality of life, and improve neurodevelopmental outcomes ***(O'Shea and Goldstein, 2003).***

Brain injury secondary to perinatal problems is a common cause of severe, long-term neurologic deficits in newborns ***(Volpe, 2008).*** Hypoxic-ischemic encephalopathy (HIE) occurs with an incidence of 1 to 4 cases per 1000 live births ***(Vannucci, 2001).***

Reviews of early intervention studies in high-risk populations have demonstrated the potential to improve long-term cognitive and psychosocial development in children ***(Grantham-McGregor et al, 2007, Walker et al, 2007 and Maulik and Damstedt, 2009).***Without these services, most children with neurodevelopmental impairments are likely to progress to more permanent functional limitations, disabilities

and handicaps ***(International Classification of Functioning Disability and Health, 2001).***

There is a need for standardized assessment tools to identify children who are at risk for neurodevelopmental impairments so that intervention may be started as early as possible **.**Adequate neurodevelopmental assessment for example Bayley Scales of Infant Development , when linked to early intervention programs has the potential to reduce disability-adjusted life-years ***(Khan et al., 2010).***

Aim of the Work

The study intended to evaluate the neurodevelopmental outcome predictive value of Clinical risk index for babies score (CRIB) at birth in Hypoxic ischemic encephalopathy (H.I.E) infants. Also, the diagnostic value of Early Motor Pattern Profile (EMPP) for motor handicap will be compared to the Bayley Scale of Infants & Toddlers Development Third edition (Bayley III).

Chapter one

Hypoxic Ischemic Encephalopathy

Introduction

Perinatal asphyxia (PA) or neonatal hypoxia- ischemia (HI) is a temporary interruption of oxygen availability that implies a risky metabolic challenge, even when the insult does not lead to a fatal outcome ***(Marschitz et al., 2011).***

Although the exact cause is not always identified, antecedents include cord prolapse, uterine rupture, placental abruption, placenta previa, maternal hypotension, breech presentation or shoulder dystocia ***(Allen and Brandon, 2011).***

The guidelines of the American Academy of paediatrics (AAP) and the American College of Obstetrics and Gynaecology consider all of the following criteria in diagnosing asphyxia:

1. Profound metabolic or mixed acidemia (pH <7.00) in umbilical artery blood sample, if obtained,
2. Persistence of an Apgar score of 0–3 for longer than 5 min,
3. Neonatal neurologic sequelae (e.g., seizures, coma, hypotonia),
4. Multiple organ involvement (e.g., kidney, lungs, liver, heart, intestines).

(American College of Obstetrics and Gynecology, 2003)

Definitions

- ***Perinatal Asphyxia***

Refers to condition during the first and second stage of laborin which impaired gas exchange leads to fetal hypoxemia and hypercarbia.It is identified by fetal acidosis as measured in umbilical arterial blood.

- ***Perinatal hypoxia, ischemia, and asphyxia***

These pathophsiologic terms describe respectively, lack of oxygen, blood flow, and gas exchange to fetus or newborn.

- ***Hypoxic–ischemic encephalopathy (HIE)***

It is a term that describes encephalopathy with objective data to support a hypoxic-ischemic mechanism as the underlying cause for the encephalopathy.HIE, also known as neonatal encephalopathy ***(Hansen and Soul, 2012).***

- ***Neonatal encephalopathy***

It is clinically defined as syndrome of disturbed neurological function in an infant's at or near term during the first week after birth, manifested by difficulty with initiating and maintaining respirations, depression of reflexes, altered level of consciousness and often seizures.

- ***Hypoxic–ischemic(HI) brain injury***

Refers to neuropathology attributable to hypoxic and /or ischemia as evidenced by biochemical (such as serum creatine kinase brain bound (CK-BB), electro physiologic (EEG), neuroimaging (head ultrasonography, magnetic resonance imaging (MRI), computed tomography (CT), or pathologic (postmortem) abnormalities ***(Ray, 2013).***

Incidince

The international incidence has been reported as 2–6/1,000 term births, reaching higher rates in developing countries ***(Kurinczuk et al., 2010).***

HIE occurs in ~2% of full term infants and in ~60% of premature newborns ***(Lai and Yang, 2011).***

Etiology

The factors causing hypoxia are divided into fetal factors and postnatal factors:

a) Fetal factors:

Fetal hypoxia may occur due to inadequate oxygenation of maternal blood as in low maternal blood pressure, inadequate relaxation of the uterus, premature separation of placenta, umbilical cord knotting or compression, impedance of blood flow

through umbilical cord and placental insufficiency due to toxemia or post maturity.

b) Postnatal factors:

Postnatal hypoxia may occur due to severe anemia (i.e. Hemorrhage or Hemolysis), severe shock (i.e. overwhelming infection, massive blood loss or adrenal hemorrhage) and inadequate oxygenation (i.e. pulmonary disease, cyanotic congenital heart disease or cerebral defect) ***(Chapman et al., 2008).***

Risk factors

Preconceptual

IDDM, thyroid disease, fertility treatments, nulliparity and advanced maternal age.

Prenatal

Pre-eclampia, smoking, diabetes, chronic hypertension, premature rupture membrane, infection, placental insuffiencey, chronic illness such as cardiopulmonary disease & chronic renal failure, antepartum haemorage, iugr, injury during pregnancy,maternal age < 15 or >35 years and substance abuse during pregnancy.

Intrapartum

Abnormal fetal presentation, prolapsed cord, umbilical cord occlusion, abruption placenta, placenta praevia, induction of labour, instrumentation and maternal pyrexia.

Preinatal

Prematurity/Postmaturity, respiratory distress syndrome, patent ductus arterious, growth retardation, fetal distress (heart rate <100), intraventricular hemorrhage, seizures, multiple births, polyhydramnios, congenital anomalies, meconium staining / aspiration, hyperglycemia /hypoglycemia, hyperthermia /hypothermia, hypercalcemia /hypocalcemia, hyperbilirubinemia and repetitive injures ***(Spitzmiller et al., 2007).***

Pathophysiology

When the placental oxygen supply is interrupted the fetus initiates breathing movements as figure (1) should these fail to provide an alternative oxygen supply, the baby loses consciousness. If hypoxia continues the respiratory center become unable to continue initiating breathing & breathing stops, usually within 2-3 minutes (primary apnea). After a latent period of apnea (primary), which may vary in duration, primitive spinal centers are no longer suppressed by the respiratory centre so exerts an effect by initiating primitive gasping breaths. After a while, if hypoxia continues, even these activities cease (terminal apnea). The time taken for such activity to cease is longer in the newly born baby than in later life, taking up to 20 minutes ***(Samuel & Wieteska, 2011).***

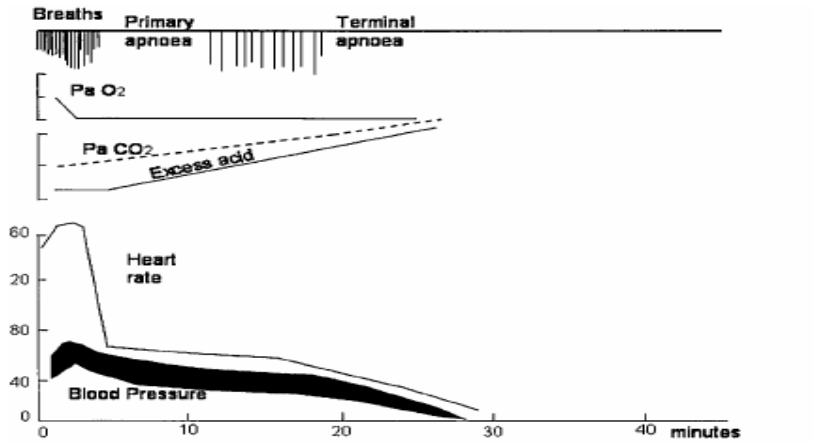

Figure (1): Response of a fetus to total, sustained asphyxia started at time 0 ***(Samuels &Wieteska et al., 2011)***

Brain hypoxia and ischemia due to systemic hypoxemia, reduced cerebral blood flow, or both are the primary physiological processes that lead to hypoxic-ischemic encephalopathy. The initial compensatory adjustment to an asphyxial event is an increase in cerebral blood flow due to hypoxia and hypercapnia. This is accompanied by a redistribution of cardiac output to essential organs, including the brain, heart, and adrenal glands. With prolonged asphyxia insult and failure of compensatory mechanisms, cerebral blood flow falls, leading to ischemic brain injury. This leads to intracellular energy failure which is also known as "primary energy failure.

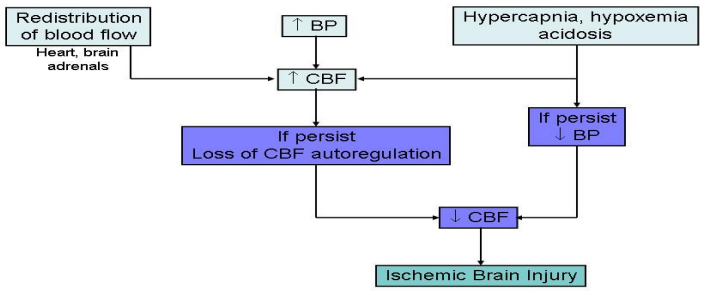

Figure (2): Fetal response to asphyxia illustrating the initial redistribution of blood flow to vital organs. With prolonged asphyxial insult and failure of compensatory mechanisms, cerebral blood flow falls, leading to ischemic brain injury ***(Mahajan and Wazir, 2011).***

Primary Energy Failure

During the early phases of brain injury a large cascade of events follows hypoxic ischemic encephalopathy injury which includes:

- Excitatory amino acid (EAA) receptor over activation including N-methyl-D-aspartate (NMDA), amino-3-hydroxy-5-methyl-4 isoxazole propionate (AMPA), and kainate receptors.
- Impaired uptake of glutamate
- NMDA receptors are permeable to Ca++ and Na+, whereas amino-3-hydroxy-5-methyl-4 isoxazole propionate (AMPA) and kainate receptors are permeable to Na+. Accumulation of Na+ coupled with the failure of energy dependent enzymes Na+/K+ - ATPase leads to rapid cytotoxic edema

and necrotic cell death. Consequences of increase of intracellular Ca2+ accumulation include activation of phospholipases, endonucleases, proteases, and in select neurons nitric oxide synthase (NOS).Activation of phospholipase A2 leads to release of Ca2+ from endoplasmic reticulum via activation of phospholipase C.Activation of protease and endonucleases result in cytoskeletal & DNA damage.

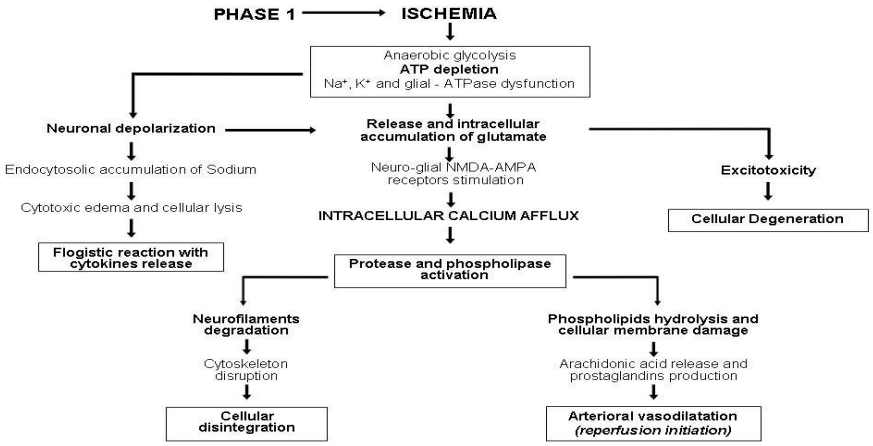

Figure (3): Primary energy failure (Phase 1) ***(Distefano and Praticò, 2010).***

Reperfusion energy

During the reperfusion period, free radicals production increases due to activation of enzyme such as cyclooxygenase, xanthine oxidase, and lipooxygenase. Free radical damage is further exacerbated in the neonate because of immature antioxidant defenses. Free radicals can lead to lipid

peroxidation as well as DNA and protein damage and can trigger apoptosis. Finally, free radicals can combine with nitric oxide (NO) to form peroxynitrite a highly toxic oxidant. NO production plays an important role in the pathophysiology of perinatal hypoxic ischemic brain injury.

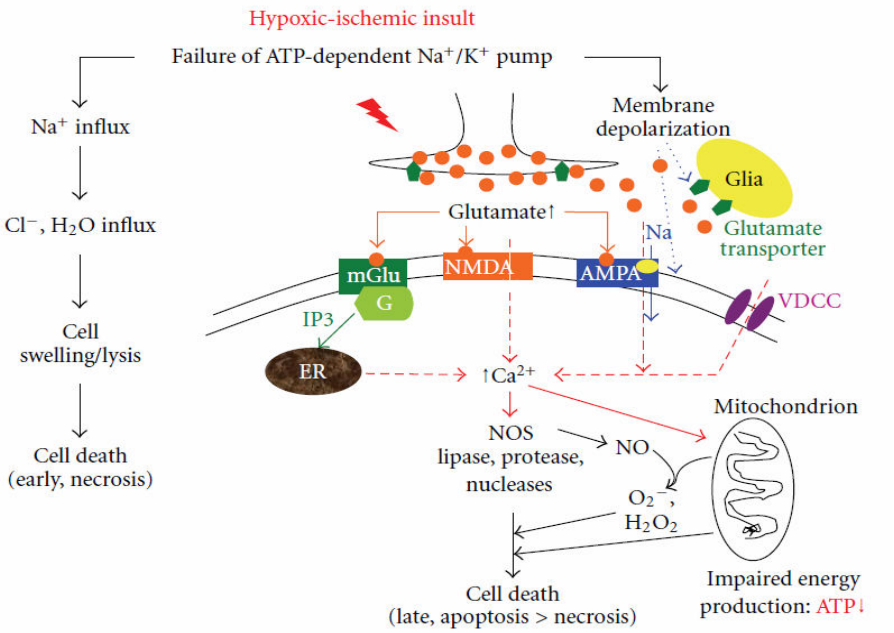

Figure (4): Relation between energy depletion and cell death.

(Lai and Yang, 2011)

Secondary energy failure

Cerebral metabolism may recover following reperfusion.This new phase of neuronal damage, starting at about 6 to 24 hours after the initial injury, is characterized by mitochondrial dysfunction and initiation of the apoptotic cascade. This phase has been called" The delayed phase of neuronal injury". The duration of the delayed phase is not precisely known in the human fetus and newborn but appears to increase over the first 24 to 48 hours and then starts to resolve thereafter.

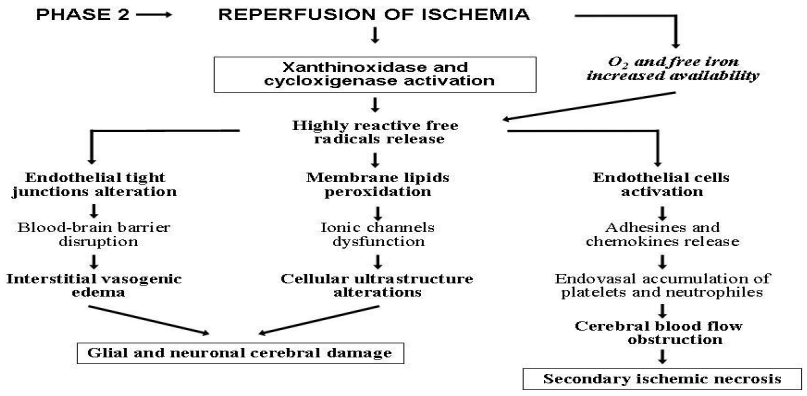

Figure (5): Secondary energy failure (Phase 2).

(Distefano and Praticò, 2010)

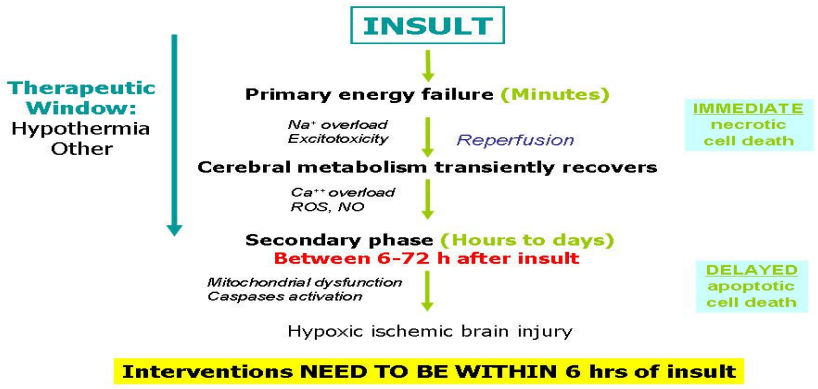

Figure (6): Pathophysiology of hypoxic-ischemic brain injury in the developing brain. During the initial phase of energy failure, glutamate mediated excitotoxicity and Na+/K+ ATPase failure lead to necrotic cell death. After transient recovery of cerebral energy metabolism, a secondary phase of apoptotic neuronal death occurs. ROS = Reactive oxygen species

(Mahajan and Wazir, 2012)

Effects of perinatal asphyxia

a) Central nervous system (CNS) &Renal effects:

Lesions most commonly seen in term infants are selective neuronal necrosis, focal and multifocal ischemic brain injury, parasagittal cerebral injury. Status marmoratus and periventricular leukomalacia were the most common lesion seen in premature infants ***(Grow & Barks, 2002).***

The kidneys seem to be the second most common target of hypoxic ischemic disease after the CNS ***(Cornette and Levene, 2009).***

b) Cardiovascular effects:

Asphyxia may cause myocardial ischemia, which usually is transient, but may rarely result in cardiogenic shock and death ***(Levene & DeVries, 2011).***

c) Pulmonary effects:

This includes increased pulmonary vascular resistance leading to persistent pulmonary hypertension (PPHN), pulmonary hemorrhage and pulmonary edema due to cardiac dysfunction, and meconium aspiration ***(Hansen and Soul, 2012).***

d) Gastrointestinal& Hepatic effects:

Asphyxiated babies are more likely to have abnormalities in intestinal motility with intolerance of entral feeding ***(Cornette & Levene, 2009).***

Ischemia can interfere with synthetic, excretory, and detoxifying functions of the liver. These functions should be assessed ***(Karlsson et al., 2006).***

e) Hematological effects:

Infants with perinatal asphyxia may have bleeding disorders include disseminated intravascular coagulation (DIC), impaired synthesis of clotting factors, and thrombocytopenia ***(Shankaran et al., 2005).***