Hypoxic Ischemic Encephalopathy (Overall view)

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M.D. degree in pediatrics
presented by

Nevine Gamal Andrawes

(M.Sc)
Faculty of Medicine — Ain Shams University
Supervised by

Prof. Dr. Iman Abdel Salam Seoud
Professor of Pediatrics
Faculty of Medicine - Cairo University
Head of Neonatology Department

Prof. Dr. Maha Mohamed Ghobashi
Professor of Public Health and Community Medicine
Faculty of Medicine - Cairo University

Assist . Prof . Dr. Hala Mufeed Said
Assistant Professor of Pediatrics
Faculty of Medicine - Cairo University

Faculty of Medicine - Cairo University
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Abstract

Introduction: Hypoxic-ischemic encephalopathy (HIE) describes the abnormal neurological state occuring in a newborn infant following a significant hypoxic- ischemic insult. The insult may occur antenatally, intrapartum or less commonly postnatally. In addition to signs of major CNS dysfunction, the affected infants may have problems with the pulmonary, cardiovascular, gastrointestinal and renal systems. Management involves prevention, adequate resuscitation, oxygenation, severity assessment and supportive management. **Objectives** :The aim is to study the differents risk factors , clinical presentations , complications , management and outcome of HIE patients in Cairo University NICU over one year starting from 1/4/2004 to 31/3/2005 with a comparative look between El Kasr El Eini and El Mounira as regards all these issues . **Patients and Methods** :Descriptive study involving all hypoxic ischemic neonates admitted into NICU of Cairo University Hospitals (El Kasr El Eini and Mounira),from l-4-2004to 31-3-2005 using SPSS version 15 to conduct analysis on IBM -compatible computer .**Results:** there was significant difference between both hospitals as regards : maternal medical and obstetric problems as anemia, multiple births, obstructed labour , fetal bradycardia and ROM > 24 hrs; fetal presentation and mode of delivery ;birth weight; Apgar score at 1 min; place of delivery ; symptomatology of patients : convulsions and respiratory distress ;outcome of ventilated HIE patients and their total mortality .**Conclusion:** the outcome was death in 42.7 % versus 57.3 % alive reflecting that prevention of HIE is definitely better than managing this neurological problem .

Key Word
HIE, Perinatal Asphyxia

CONTENTS

LIST OF ABBREVIATIONS

ATN	: acute tubular necrosis
ATP	: adenosine triphosphate
AAP	: American Academy of Pediatrics
ACOG	: American College of Obstetrics and Gynecologists
a EEG	: amplitude integrated EEG
ABP	: arterial blood pressure
BUN	: blood urea nitrogen
Ca^{2}	: calcium
Cal	: calories
CTG	: cardiotocography
CNS	: central nervous system
CVP	: central venous pressure
CBF	: cerebral blood flow
CP	: cerebral palsy
CPP	: cerebral perfusion pressure
CSF	: cerebrospinal fluid
CBC	: complete blood picture
CT	: computed tomography
C-RP	: c-reactive protein
CK.BB	: creatine kinase brain fraction
c-AMP	: cyclic adenosine monophosphate
c-GMP	: cyclic guanosine monophosphate
COX-2	: cyclooxygenase-2
DNA	: deoxyribonucleic acid
DWI	: diffusion weighted imaging
DIC	: disseminated intravascular coagulation
ECG	: electrocardiogram
EEG	: electroencephalography
ER	: endoplasmic reticulum
EAA	: excitatory amino acid
FHR	: fetal heart rate
Fig	: figure
GABA	: gamma-amino butyric acid
GIT	: gastrointestinal tract
Hr	: hours
H+	: hydrogen ion
H2O2	: hydrogen peroxide
HI	: hypoxic injury
HIE	: Hypoxic ischemic encephalopathy
IGF-1	: insulin like growth factor-1

Ils : interleukins
ICP : intracranial pressure
IUGR : intrauterine growth retardation
IVH : intraventricular hemorrhage
K+ : potassium
Kg : kilogram
MRI : magnetic resonance imaging
MRS : magnetic resonance spectroscopy
mEq/L : milliequivalent per liter
mg/dl : milligram per deciliter
mg/kg : milligram per kilogram
mm^3 : cubic millimeter
mmHg : millimeter mercury
mmol/l : millimol per liter
min : minutes
Na+ : sodium
ng/ml : nanogram per milliliter
NEC : necrotizing enterocolitis
NICU : neonatal intensive care unit
NSE : neuron-specific enolase
NO : nitric oxide
NOS : nitric oxide synthase
NMDA : N-methyl D-aspartate
PN : parenteral nutrition
PTT : partial thromboplastin time
PVL : Periventricular leukomalacia
PlA2 : phospholipase A2
PAF : platelet-activating factor
PPV : positive pressure ventilation
PET : positron emission tomography
PLIC : posterior limb of internal capsule
PT : prothrombin time
RHD : rheumatic heart disease
SPECT : single photon emission tomography
SOD : superoxide dismutase
SIADH : syndrome of inappropriate antidiuretic hormone secretion
Tab : table
TGFB : Transforming growth factor beta
TNF : tumor necrosis factor
US : ultrasonography
% : percent

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Introduction and Aim of The Work

Introduction:

Hypoxic-ischemic encephalopathy (HIE) describes the abnormal neurological state occuring in a newborn infant following a significant hypoxic- ischemic insult. The insult may occur antenatally, intrapartum or less commonly postnatally. In addition to signs of major CNS dysfunction, the affected infants may have problems with the pulmonary, cardiovascular, gastrointestinal and renal systems. Hypoxic injury in fetuses and neonates reflect combinations of hypoxia and ischemia rather than hypoxia alone. A severe asphyxial injury results in a cascade of biochemical events that evolves over hours to several days. Management involves prevention, adequate resuscitation, oxygenation, severity assessment and supportive management ***(Aurora and Snyder, 2004).***

Aim of the work :

The aim is to study the different risk factors , clinical presentations , complications , management and outcome of HIE patients in Cairo University Neonatal Intensive Care Unit (NICU) over one year starting from 1/4/2004 to 31/3/2005 with a comparative look between El Kasr El Eini and Abou ElReesh as regards all these issues .

Hypoxic Ischemic Encephalopathy

Definition:

Hypoxic ischemic encephalopathy (HIE) is an important cause of mortality and morbidity in full - term newborns and neurologic handicaps that develop in 25-28% of these infants **(Nelson and Ellenberg, 1984 and Hankins and Speer, 2003) .**

Asphyxia is etymologically derived from the Greek word meaning " pulseless" but the term asphyxia has become widely used to describe a presumed intrapartum hypoxic ischemic insult **(Evans and Levene, 1999) .**

Perinatal asphyxia is an insult to the fetus due to the lack of oxygen (hypoxia) and/or lack of perfusion (ischemia) to various organs. It is associated with tissue lactic acidosis. If accompanied by hypoventilation, it may be also associated with hypercapnia **(Evans and Levene, 1999 and Aurora and Snyder,2004).** The effect of hypoxia and ischemia may not be identical , but they are difficult to separate clinically.Both factors probably contribute to injury **(Snyder and Cloherty, 2004) .**

Concerning definition of perinatal asphyxia, there is no single tool that can yield a precise definition , but recently, the American Academy of Pediatrics (AAP) and the American College of Obstetrics and Gynecologists (ACOG) committees on Maternal Fetal Medicine and Fetus 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 acidemia pH < 7.00 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 (e.g., seizures, hypotonia, coma or HIE) .
4.Evidence of multiorgan system dysfunction in the immediate neonatal period .

(AAP and ACOG , 1996 ; Sills, 2004)

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 7.00, persistence of an Apgar score of 0 to 3 for greater than 5 min, and presence of meconium and placental pathology that may or may not be evident on gross inspection **(Korthals and Colon,2005) .**

Incidence :

Hypoxic ischemic insult is an important cause of death and disability. In Egypt and other developing countries, perinatal asphyxia is the most important cause of hypoxic ischemic brain damage in the full - term newborn infants. HIE is known to lead to a higher morbidity and mortality among these infants **(Boo et al, 2000).** The incidence of perinatal asphyxia is about 1.0 to 1.5% in most centers and is usually related to gestational age and birth weight. It occurs in 9% of infants less than 36 weeks gestation **(Legido et al., 2000),** and in 0.5% of infants more than 36 weeks gestation accounting for 20% of perinatal deaths or as high as 50 % of deaths if stillborns are included **(Levene, 1995 and**

Aurora and Snyder, 2004). The incidence is higher in term infants of diabetic or toxemic mothers. These factors correlate less well in preterm infants . Intrauterine growth retardation and breech presentation are associated with an increased incidence of asphyxia. Postmature infants are also at risk **(Aurora and Snyder,2004)** .

Causes of Hypoxic-Ischemic Encephalopathy :

There are multiple causes of asphyxia **(Table 2)** , and they may be related to the maternal factors, placenta, umbilical cord, fetus, or infant **(Behrman et al.,2004).**Most cases of HIE result from injury in the prenatal period secondary to intrauterine asphyxia **(Table2)** , with disturbance of gas exchange across the placenta and with respiratory failure at birth. Postnatally, respiratory insufficiency caused by acute respiratory distress syndrome, recurrent apneic spells, severe cardiac right-to-left shunt, or persistent fetal circulation can cause HIE. Since neonatal brain tolerance to severe hypoxia and ischemia is different from that of older children, this review focuses on HIE from causes during prenatal, perinatal, and neonatal period **(Korthals and Colon, 2005) .**

Table (2): Etiologies of perinatal asphyxia. Adapted from **Gabbe SG, Behrman RE.**

Source	Etiologies
Maternal	Hypotension secondary to hemorrhage, spinal anesthesia, compression of the vena cava and aorta by the gravid uterus, or from other medical conditions, hypoventilation during anesthesia, maternal lung disease, diabetes, hypertension, prolonged rupture of membranes.
Placenta	Premature placental separation, inadequate relaxation of the uterus to permit placental filling due to oxytocin induced tetany, uterine vessel vasoconstriction by cocaine, placental insufficiency from toxemia, postmaturity or other medical condition.
Umbilical cord	Cord compression, knot, failure to properly clamp the cord .
Infant	Failure to execute proper resuscitation ,cyanotic heart disease, respiratory failure or distress, meconium aspiration syndrome, prematurity, multiple births, breech presentation, growth retardation, fetal anomalies, and Rhesus isoimmunization.

(Gabbe et al., 2002 and Behrman et al.,2004)

Another classification : **Stoll and Kliegman, (2004)** divided the etiological factors into fetal and neonatal causes.

A) Fetal hypoxia which may be caused by :

1. Inadequate oxygenation of maternal blood due to hypoventilation during anesthesia , cyanotic heart disease, respiratory failure, or carbon monoxide poisoning.

2. Low maternal blood pressure as a result of hypotension that may complicate spinal anesthesia or that may result from compression of the vena cava and aorta by the gravid uterus.

3. Inadequate relaxation of the uterus to permit placental filling as a result of uterine tetany caused by excessive administration of oxytocin .

4. Premature separation of placenta.

5.Impedance to the circulation of blood through the umbilical cord as a result of compression or knotting of the cord.

6. Uterine vessel vasoconstriction by cocaine.

7. Placental insufficiency from numerous causes including toxemia and postmaturity.

B) Neonatal hypoxia which may be caused by :

1. Anemia severe enough to lower the oxygen content of the blood to a critical level owing to severe hemorrhage or hemolytic disease.

2. Shock severe enough to interfere with the transport of oxygen to vital cells from overwhelming infection, massive blood loss and intracranial or adrenal hemorrhage.

3. A defect in arterial oxygen saturation resulting from failure to breath adequately postnatally owing to cerebral defect, narcosis, or injury.

4. Failure of oxygenation of an adequate amount of blood resulting from severe forms of cyanotic congenital heart disease or pulmonary disease.