PREDICTIVE VALUE OF SEVERAL BIOCHEMICAL MARKERS FOR NEURODEVELOPMENTAL OUTCOME AFTER BIRTH ASPHYXIA

Essay

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بسم الله الرحمن الرحيم

قالوا سبحانك لا علم لنا إلا ما علمتنا
إنك أنت العليم الحكيم

صدق الله العظيم

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Abstract

Perinatal asphyxia continues to be a major cause of neonatal morbidity, mortality and neurodevelopmental disability.

In spite of major advance in monitoring technology and knowledge of fetal and neonatal pathologies, perinatal asphyxia or, more appropriately hypoxic-ischemic encephalopathy (HIE), remains a serious condition, causing significant mortality and long-term morbidity.

Understanding the timing of the insult and contributing factors may be improved by adequate documentation of general medical and obstetric factors, determination of pH and blood gases in the cord blood and neonatal Neuro- imaging.

Other diagnostic tools of crucial importance to predict the neurologic outcome after cerebral injury are measurements of markers of perinatal brain injury in biological fluids with the aim of improving the ability to detect fetuses and newborns at risk of brain injury at an earlier stage, when the window for therapeutic actions is still open.

The aim of the work is to provide insight into the role of different biochemical markers and their reliability as indicators of hypoxic ischemic encephalopathy and to show whether detection of elevated serum concentrations of these proteins reflects long term neurodevelopmental impairment or not.

Key Words : Perinatal asphyxia – Hypoxic-ischemic encephalopathy – Hypoxia – Ischemia – Protein S100 B – Creatine kinase BB – Neuron specific enolase – Erythropoietin – Interleukin 18

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LIST OF ABBREVIATIONS

^{1}H NMR	*Proton nuclear magnetic resonance*
AAP	*American Academy of Pediatrics*
ACOG	*American College of Obstetricians and Gynecologist*
ADH	*Antiduretic hormone*
ADP	*Adenosine di phosphate*
ALT	*Alanine transaminase*
AMP	*Adenosine mono phosphate*
AMPA-QA	*A- amino-3- hydroxyl-5-methyl-4-isoxazole propionate*
APUD	*amine precursor uptake and decarboxylation*
AST	*Aspartate transaminase*
ATP	*Adenosine triphosphate*
AVP	*Arginine vasopressin*
B2M	*B2 microgloblin*
BBB	*Blood Brain Barrier*
CA	*Cardiac arrest*
Ca+	*Calcium*
CAMP	*Cyclic adenosine mono phosphate*
CBF	*Cerebral blood flow*
CK-BB	*Creatine kinase BB*
Cl-	*Chloride*
CNS	*Central nervous system*
CO	*Carbon monoxide*
COP	*Cardiac out put*
CP	*Cerebral Palsy*
CSF	*Cerebrospinal fluid*

CT	*Computerized tomography scan*
CTG	*Cardiotocography*
DIC	*Disseminated intravascular coagulopathy*
DNA	*Deoxy ribonucleic acid*
EEG	*Electroencephalography*
EPO	*Erythropoietin*
GFAP	*fibrillary acidic protein*
GGT	*Gamma glutemyl Transferase*
GIT	*Gastrointestinal tract*
HbCO	*Carboxy hemoglobin*
HI	*Hypoxia ischemia*
HIE	*hypoxic ischemic encephalopathy*
HIF-1	*Hypoxia inducible factor 1*
HIF-2	*Hypoxia inducible factor 2*
HIF HMAO	*hexamethylaminoxine*
HO	*Heme oxygenase*
HX	*Hypoxanthine*
ICH	*Intracranial hemorrhage*
IFN-	*Interferon*
IGF-1	*Insulin-like growth factor 1*
IL-18	*Interleukin 18*
IL-6	*Interleukin 6*
IMP	*iodinated phetamine*
IPPV	*intermittent positive pressure ventilation*
IUGR	*Intrauterine growth retardation*
KA	*Kainic acid*
LBW	*Low birth weight*
LDH	*Lactate dehydrogenase*

mm Hg	*mm mercury*
MRI	*Magnetic resonance imaging*
MRS	*Magnetic resonance spectroscopy*
Na+	*Sodium*
NK	*Natural killer cells*
NMDA	*N-methyl-D-aspartate*
NO	*Nitric oxide*
NOS	*Nitric oxide synthase*
NSE	*Neuron specific enolase*
P.Cr.	*Phospho creatine*
PET	*Positron emission tomography*
Pi	*Inorganic phosphate*
PT	*Prothrombine time*
PTT	*Partial thromboplastin time*
PVL	*Periventricular leukomalacia*
QA	*Quisqualic acid*
S-100B	*S100 protein*
SPECT	*Single photon emission computed tomography*
Tc99	*Technetium 99*
TCK	*Total creatine kinase*
Th1	*T helper 1*
TNF	*Tumor necrosis factor*
US	*Ultrasound scan*
SIADH	*Inappropriate secretion of antidiuretic hormone*

INTRODUCTION AND AIM OF THE WORK

Perinatal asphyxia continues to be a major cause of neonatal morbidity, mortality and neurodevelopmental disability ***(Thorngren et al., 2003).***

In spite of major advance in monitoring technology and knowledge of fetal and neonatal pathologies, perinatal asphyxia or, more appropriately hypoxic-ischemic encephalopathy (HIE), remains a serious condition, causing significant mortality and long-term morbidity. HIE is an acquired syndrome characterized by clinical and laboratory evidence of acute brain injury due to asphyxia (i.e., hypoxia and acidosis) ***(Raju, 2006).***

Neonatal brain injury occurs most frequently after a perinatal hypoxic-ischemic insult. Current data suggest that about 2 to 5 of 1,000 live births in United States and more so in developing countries experience a brain injury. Approximately 20% to 40% of infants who survive the brain injury develop significant neurological and developmental impairment ***(Badr Zahr and Purdy, 2006).***

Contribution of asphyxia at birth to cerebral palsy in infants born at term varies from 8% to 28%. Preterm birth accounts for most cases of perinatal mortality and about 40% of neurologically handicapped children. In preterm infants, 60% of neurologic handicaps are attributable to peri/neonatal events, 10% are of antenatal origin and 30% are of generally unknown origin. In infant born at term, 50% of cases of cerebral palsy have a prenatal etiology, 36% are of peri/neonatal origin, and 14% of cases are of unknown etiology ***(Michetti and Gazzolo, 2002*).**

School-aged children with a history of moderately severe HIE, 15-

20% had significant learning difficulties, even in the absence of obvious signs of brain injury. All children who have moderately severe or severe HIE as infants should be monitored well into their school-age years ***(Zahra and Moataza, 2001).***

Target organs of perinatal asphyxia include the brain, heart, lung, kidney, bowel and bone marrow. The most frequent abnormalities in perinatal asphyxia involve the kidney (50%) followed by the central nervous system (28%). Understanding the timing of the insult and contributing factors may be improved by adequate documentation of general medical and obstetric factors, determination of pH and blood gases in the cord blood and neonatal Neuro- imaging ***(Volpe, 2001).***

Other diagnostic tools of crucial importance to predict the neurologic outcome after cerebral injury are measurements of markers of perinatal brain injury in biological fluids with the aim of improving the ability to detect fetuses and newborns at risk of brain injury at an earlier stage, when the window for therapeutic actions is still open. ***(Nagdyman et al., 2001).***

Previously published studies demonstrated that S-100B, CK-BB and NSE are reliable indicators of hypoxic ischemic encephalopathy after birth asphyxia; whether detection of elevated serum concentration of these proteins reflects long term neurodevelopmental impairment remains to be investigated ***(Nagdyman et al., 2003).***

Aim of the Work

To provide insight into the role of different biochemical markers and their reliability as indicators of hypoxic ischemic encephalopathy and to show whether detection of elevated serum concentrations of these proteins reflects long term neurodevelopmental impairment or not.

Perinatal Asphyxia

Definition

Perinatal asphyxia is an insult to the fetus or the newborn due to lack of oxygen (hypoxia) and / or lack of perfusion (ischemia) to the various organs ***(Vannucci and Hagberg, 2004).***

Hypoxemia is defined as diminished oxygen content of blood. Ischemia is characterized by reduced blood perfusion in a particular tissue bed. In most instances, during the perinatal period, hypoxemia or ischemia or both occur as a result of asphyxia which denotes an impairment in gas exchange, that results not only in a deficit of oxygen in the blood but also an excess of carbon dioxide and thereby acidosis ***(Lynam and Verklan, 2004).***

Volpe (2001) concluded that ischemia is more important than hypoxia. With ischemia, the brain lacks a supply of both oxygen and glucose which increase the likelihood of brain injury.

Concerning definition of perinatal asphyxia there is no single tool or test which can yield a precise definition, but the ***American Academy of Pediatrics (AAP) and the American College of Obstetrics and Gynecology (ACOG) (2006)*** defined certain criteria that's to be present to confirm the occurrence of perinatal asphyxia and predict the possibility for resultant neurologic deficits (table 1). In cases in which such evidence is lacking, it cannot be concluded that perinatal asphyxia exists.

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 to3 >5 minutes.
3. Clinical neurologic sequelae in the immediate neonatal period (e.g., seizure, hypotonia, coma or HIE).
4. Evidence of multiorgan system dysfunction in the immediate neonatal period.

(AAP and ACOG, 2006).

1. Acidemia

In utero, varying degree of hypoxia and transient interference with maternal fetal respiratory exchange are common in all labors (Table 2). However, if significant hypoxemia occurs, the fetus will utilize anaerobic glycolysis to meet its energy needs. The subsequent formation of non volatile acids, such as lactic acid will result in a decrease in the blood pH of the fetus and lactic acidosis. This can be classified as respiratory, metabolic or mixed acidemia (table 3) ***(Stoll and Kliegman, 2004).***

Table (2): Normal blood gas values in term newborn

	At birth			**At age**		
	Maternal artery	Umbilical vein	Umbilical artery	10 min umb.artery	30 to 60 min umb.artery	5 hr
PO_2	95	27.5	16	50	54	74
PCO_2	32	39	49	46	38	35
pH*	7.4	7.32	7.24	7.21	7.29	7.34

(Snyder and Cloherty, 2004).

pH*: a scalp pH in labor of 7.25 or above is considered normal.

The normal umbilical artery pH is 7.25 to 7.35, but a pH 7.25 to 7.20 is considered pre acidosis and < 7.20 is considered acidosis.

Table (3): Types of acidemia

a. Respiratory acidemia	PCO_2 is high HCO_3 is normal
b. Metabolic acidemia	PCO_2 is normal HCO_3 is low
c. Mixed acidemia	PCO_2 is high HCO_3 is low

(Borruto et al., 2006).

2. Apgar score

In 1952, Dr Virginia Apgar devised a scoring system that was a rapid method of assessing the clinical status of the newborn infant at 1 minute of age and the need for prompt intervention to establish breathing ***(Apgar, 1953).***

The Apgar score is used to assess the state of the newborn during the first critical minutes of life and comprises 5 components: heart rate, respiratory effort, muscle tone, reflex irritability, and color, each of which is given a score of 0, 1, or 2. Each component of the Apgar score carries the same weight in the assessment and therefore contributes equally to the total score. The most important of the signs is the heart rate which indicates life or death. Respiratory effort, tone and reflex irritability, were found to closely correlate with each other and with total score. Color correlated most poorly among the other components ***(AAP and AHA, 2005)***.

Apgar scoring system can be summarized as shown in (Table 4).