Prognostic Value of Neuron Specific Enolase in Preterm Neonates

Thesis
Submitted for the partial fulfillment of
Master degree in **Pediatric Medicine**

By
Seham Mansour Elbehery
M.B., B.Ch. 2003 Tanta University

Under the supervision of

Prof. / Sahar M. A. Hassanein
Professor of Pediatrics
Faculty of Medicine - Ain Shams University

Prof. / Safaa Shafik Emam
Professor of Pediatrics
Faculty of Medicine - Ain Shams University

Prof. / Hanaa Ahmed Amer
Professor of Clinical Pathology
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University

2012

القيمة التنبؤية للاينولاز الخاص للخلية العصبية فى الأطفال المبتسرين

رسالة
توطئة للحصول على درجة الماجستير **فى طب الأطفال**

مقدمة من
الطبيبة / سهام منصور البحيرى
بكالوريوس الطب والجراحة ٢٠٠٣
جامعة طنطا

تحت إشراف

أ.د/ سحر محمد أحمد حسنين
أستاذ طب الأطفال
كلية الطب - جامعة عين شمس

أ.د/ صفاء شفيق إمام
أستاذ طب الأطفال
كلية الطب ـ جامعة عين شمس

أ.د/ هناء أحمد عامر
أستاذ الباثولوجيا الاكلينيكية
كلية الطب ـ جامعة عين شمس

كلية الطب
جامعة عين شمس
٢٠١٢

Summary and conclusion

The present work aims to study and evaluate NSE as predictor and prognostic marker of intraventricular / periventricular hemorrhage in preterm infants.

This case control study was conducted on **58** neonates, **30** preterm neonates and **28** full term neonates. 8 of 30 preterm infants **(26.6%)** got IVH while none of 28 full term infants got IVH. Preterm infants with IVH, their gestational age ranged from 28-33 weeks, birth weight ranged from 500-2300gm, **87.5%** of them were males, **62.5%** of which delivered vaginally and none of which was the first baby of birth.

Preterm infants without IVH were 22 infants, their gestational age ranged from 28-35 weeks, their birth weight ranged from 600-2600gm.

A thorough history was taken (prenatal, natal, postnatal).The infants were subjected to apgar score at 1 and 5 minutes, assessment of gestational age through analysis of maternal dates and Ballard scores, thorough complete clinical examination including cardiac, chest, abdominal and neurological, laboratory investigation including CBC, CRP and laboratory evaluation of NSE in cord blood was performed by ELISA technique and neonatal cranial ultrasound that done at 1,3,7 postnatal days.

Serum NSE level was statistically significant higher in preterm infants (mean ± SD 12.63 ±7.54 µg/L) compared to full term infants (mean ± SD 6.11 ± 4.54 µg/L), Z= -3.408, P <0.01.

Male sex may be more liable to birth complications as PIVH than female sex.

Statistically significant higher serum NSE was found in preterm infants with IVH (mean ± SD 21.01±3.13) compared to infants without IVH (mean± SD 9.58 ± 6.23µg/L), Z = -3.82, P <0.001.

Roc curve in the present study showed that cord blood NSE has 99.05 % specificity and 87.5 % sensitivity to predict IVH at cut off value of 18.8µg/L.

Acknowledgement

First, thanks are all due to Allah for Blessing this work until it has reached its end, as a part of his generous help throughout our life.

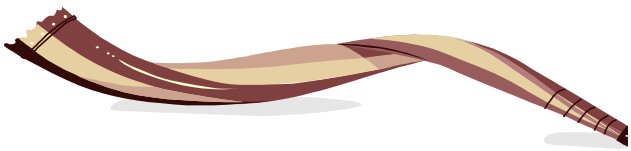
I am deeply grateful to Dr. Sahar M. A. Hassanein, Professor of Pediatrics, Faculty of Medicine, Ain Shams University for sponsoring this work, and her keen supervision, continuous encouragement and it is an honor to work under her guidance and supervision.

I am also greatly indebted to Dr. Safa Shafik Emam, Professor of Pediatrics, Faculty of Medicine, Ain-Shams University, for her great supervision, great help, available advises and continuous support.

I would like to direct my special thanks to Dr. Hanaa Ahmed Amer Professor of Clinical Pathology, Faculty of Medicine, Ain Shams University, for her invaluable help and fruitful advice.

Thanks to all patients and all house care workers for their support in this work.

I want also to thank my family for supporting me throughout my life.



Seham Mansour Elbehery

List of Tables

List of Contents

Introduction

Preterm birth is the leading cause of newborn deaths, and now is the second leading cause of death after pneumonia in children under the age of 5 years**(Born too Soon, 2012)**.

(Born too Soon, 2012) found that about 15 million babies are born too soon every year, more than 1 in 10 babies are born preterm, affecting families all around the world, more than 60% of preterm births occur in subSaharan Africa and South Asia and that75% of deaths of premature babies could be prevented without intensive care.

Preterm birth rates are increasing in almost all countries with reliable data and Global progress in child survival and health to 2015 and beyond can not be achieved without addressing preterm birth **(Born too Soon, 2012).**

Because they are born too soon, many of their biological systems, such as those involving the lungs and the liver are not developed enough to work properly on their own **(Groenendaal et al., 2010; Steinhorn, 2011)**. This can result in jaundice, breathing difficulties and C.N.S problems after they are born **(Stephens &Vohr, 2010; Guerrot & Chadie, 2012).**

Intraventricular hemorrhage (IVH) is a condition related to rupture of small vessels within the germinal matrix.IVH is more common in premature babies who have had physical stress, such as respiratory distress syndrome, pneumothorax rapid transfusion and coaguolopathy or high blood pressure **(Faroogi & Sedin, 2011).**

The most serious complication of IVH in premature infant is posthemorrhagic hydrocephalus, which is caused by multiple small clots obstructing the arachnoid villi **(Beaino& Khoshnood, 2010; Lopriore & Walther, 2011).**

The prescence of NSE in several structures and cells of cord and placenta tissue questions the validity of these proteins as neuronal marker in cord blood. Increased leakage from a damaged placenta caused by villitis or infarction may explain elevated cord blood and amniotic NSE levels and a relation with adverse neurologic outcome may be indirect rather than direct **(Elimian&Tejani, 2001).**

(Elimian& Tajani, 2001) considered NSE as one of the helpful markers of neurological injury which found to be elevated in the amniotic fluid of women whose neonates subsequently developed intraventricular hemorrhage.

Enolase is a dimetric cytoplasmic enzyme, it is predominantly found in neuronal and neuron endocrine tissues **(Yamada et al., 2011).** Cell injury causes its release into the blood and cerebrospinal fluid (CSF). Neuron Specific Enolase has been measured in the serum and CSF of adults and full-term asphyxiated neonates as a marker of neurological injury **(Giuseppe & Sergio, 2009; Brea et al., 2009; Moritz et al., 2010; Shiihara & Miyake, 2011).**

The relation between Neuron Specific Enolase and perivetricular /intraventricular hemorrhage (PIVH) in preterm neonates if confirmed might open new therapeutic and preventive aspects in this field.

Aim of TheWork

The aim of this study is to asses the role of neuron specific enolase as an early preclinical diagnostic and predictive marker for the occurrence of intraventricular / periventricular brain hemorrhage in preterm infants.

Review of Literature

Prematurity:

For more than 50 years, science has faced the challenging problem of prematurity and its impacts on the health and development of children. The gradual rise in prematurity rates is forcing clinicians, researchers and policy-makers to work together to determine what actions should be given priority in this area **(Zelkowitz et al., 2011).**

Infants born before 37 weeks from the first day of the last menstrual period are considered premature. The more preterm an infant is born, the greater the risk that the infant will experience complications of prematurity **(Eichenwald & Stark, 2008; Voss & Jungmann, 2012).**

Mortality among prematurely born infants has decreased dramatically over the past decade in developed countries. The survival rate for very-low-birth-weight (VLBW) infants (less than 1, 500 g) has risen from 50% to more than 85% since the introduction of neonatal intensive care in the early 1970s **(Fanaroff et al ., 2007).** However, a similar improvement in morbidity and long-term consequences among these very prematurely born children has not yet been conclusively shown to have taken place. Hence, there is intense ongoing research addressing possible improvements to medical treatment **(Harijan & Bear, 2012).**

Preterm birth is associated with more than one third of all infant death **(MacDorman & Mathews,2008**), and the second leading cause of death after pneuomonia in children under the age of 5 years **(Born Too Soon, 2012).**

Prematurity and low birth weight (LBW less than 2500 g) accounted for 16.5% of all infant deaths in 2005 and was the second leading cause of infant mortality **(Saigal & Doyle , 2008),** 15 million babies are born too soon every year more than 1 in 10 babies are born preterm all around the world **(Born Too soon, 2012).**

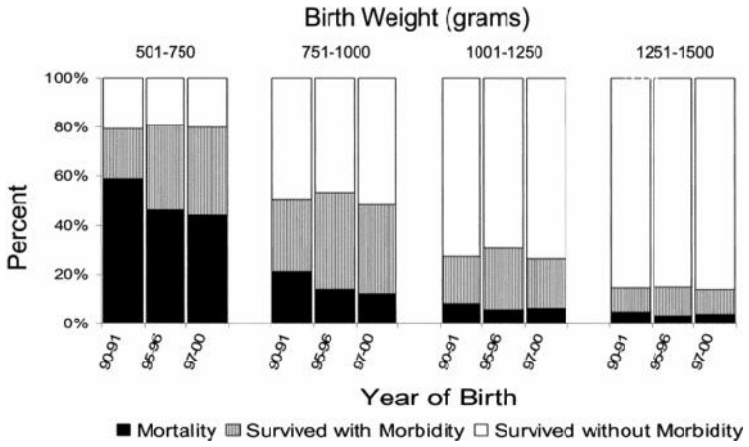


Fig (1): Birth weight and percent of neonatal morbidities and mortalities from (1990-2000) **(Fanaroff et al., 2007).**

Preterm births are at significantly increased risk of adverse neurodevelopmental sequelae **(Petrini et al., 2009;Meadow ,2012)**; although the vast majority of preterm newborn survive, studies of short and long outcomes find significantly higher rates of neurodevelopmental morbidities, sensoneural impairement and other disabilities (eg, cerebral palsy and visual, auditory and intellectual impairement) and higher rate of complications of the respiratory, gastrointestinal and renal systems **(Fanaroff et al ., 2007, Honein, 2008, Talge et al ., 2010).**

Preterm birth is a major economic burden with associated costs totaling over $26 billion in 2005 in USA **(Institute Of Medicine, 2006, McLaurin et al., 2009).**

Preterm birth accounts for half of infant hospitalization costs and one quarter of pediatric costs suggesting that major infant and pediatric cost saving could be realized by preventing preterm birth **(Russel et al., 2007).**

Three standard subdivisions classify under weight infants and three are designated for the degree of immaturity (approximate gestational age at birth). Infants born weighing less than 1000g are considered to be extremely low birth weight (ELBW). An infant born weighing between 1000 and 1500 g is considered to be very low birth weight (VLBW). Infants born weighing between 1500 and 2500 g are considered to be low birth weight (LBW) **(Subramanian, 2009; Hansen&Stoll, 2010; Jobe, 2010; Lindermann, 2012)**.

An infant born before 25 weeks gestation is referred to as being extremely preterm **(Nicholas et al., 2000).** An infant born between 25 and 32 weeks gestation is referred to as being very preterm. An infant

born from 32 to less than 37 weeks gestation is referred to as being late preterm **(Sizun&Westrup, 2004 , Hamilton et al .,2010; Hunt& Hey , 2010).**

Born Too Soon, 2012 found that subcategories of preterm birth; based on weeks of gestational age include: extremely preterm <28 weeks, very preterm (28-32) weeks, moderate to late preterm (32-37).

Incidence:

The incidence of prematurity shows variations from one area to another. In 2006, over 500.000 babies or one of every eight babies born in the United States were born premature **(MacDorman & Mathews, 2008**).

In developing countries, approximately 70 % of LBW infants have intrauterine growth retardation (IUGR), while in developed countries 30% of LBW infants have IUGR. Infants with IUGR have greater morbidity and mortality than appropriate for gestational age **(Gilbert et al., 2003; Korvenranta et al., 2009).**

World wide, an estimated 13 million babies are born preterm and, of those, one million die as a result of their early birth, according to **an October 2009 March of Dimes** report on the global toll of preterm birth.

(Stephens & Vohr , 2010) found that the estimated incidence of low birth weight infants in developed countries ranges from roughly 5% to 8% and is approximately 19% in developing countries, preterm birth estimates range between 5% and 12% in developed countries and account for 25% of births in the developing countries.

While (**Born Too Soon, 2012)** found that about 15 million babies are born too soon every year, more than 1 in 10 babies are born preterm, affecting families all around the world and more than 60% of preterm births occur in subSaharan Frica and South Asia.

Neonatal problems associated with premature infants:

Preterm infants usually show physical signs of prematurity in reverse proportion to the gestational age **(Eichenwald & Stark, 2008; Jary& Whitelaw, 2012).**

Generally, the lower the gestational age, the higher the impact on biological functions will be **(Harijan & Bear, 2012).**

Infants who are <1500 g are more likely to experience significant medical complications, such as severe respiratory distress, haemorrhages in the brain, and poorer nutrition, all of which may have long-lasting effects on the central nervous system. Among VLBW infants, about 10% will have cerebral palsy and 15% will have an IQ in the mentally deficient range **(Rameix &Moriette, 2010**).

Premature infants are also at increased risk for congenital malformations, hearing and visual deficits, reactive airway disease and growth failure and. These biological effects are compounded by social risk factors, which are more prevalent among families of infants who are born prematurely (**Petrini et al., 2009; Shah & Sankaran, 2012).**

A) Nervous system:

It has long been established that premature infants are at higher risk of developmental problems. These problems are linked to the fact that biological functions (such as the central nervous system and lungs) were unable to reach complete maturity during pregnancy **(Patrizini, 2010).**

Incidentally, after birth, the interaction between this biological immaturity and the physical and social environment of the child plays a crucial role in his or her development **(Stephens&Vohr, 2010).**

Neurodevelopmental problems include apnea of prematurity**,** retinopathy of prematurity, developmental disabilities, cerebral palsy and intraventricular hemorrhage. The latter affecting 25 percent of babies born usually before 32 weeks of pregnancy (**Brouwer et al ., 2008; March of Dimes, 2009**), mild brain bleeds usually leave no few lasting complications, but severe bleeds often result in brain damage or even death **(Shankaran , 1997 ; March of Dimes, 2009;Meyer Schiffer & Leone ,2011).**

Also, hypoxic ischemicencephalopathy, periventricular leukomalacia, seizures, hypotonia, deafness, congenital malformations and kernicterus (bilirubin encephalopathy)**(Hansen&Stoll, 2010).**

B) Cardiovascular system:

Failure of the ductus arteriosus to close after birth (patent ductus arteriosus), hypotension, hypertension, bradycardia (with apnea), congenital malformations are the main cardiovascular complications in preterm infants **(Hansen&Stoll, 2010; Shah& Sankaran, 2012).**

C) Respiratory system:

Respiratory problems are common specifically the respiratory distress syndrome (previously called hyaline membrane disease), brochchopulmonary dysplasia (BPD) **(Hibbard&Wilkins, 2010; Laughon&Bose, 2011),** also, pneumothorax, interstitial emphysema, congenital pneumonia, pulmonary hypoplasia and pulmonary hemorrhage **(Stephens & Vohr, 2010).**

D) Hematological problems in premature infants:

Anemia of prematurity, hyperbilirubinemia –indirect or direct, dissiminated intravascular coagulopathy, also subcutaneous and organ (liver, adrenal) hemorrhage, vitamin k deficiency and hydrops (immune or non immune)**(Hansen&Stoll, 2010).**

E) Gastrointestinal system:

The ability to suck, swallow and breath in a coordinated fashion is not in place until 34-36 weeks of gestation, so entral feeding must be provided by gavage **(Gewolb&Bosma, 2001).**

Furthermore, preterm infants frequently have gastro osophagel reflux and immature gag reflex, which increases the risk of aspiration of feeding **(Golski&Rom, 2010)**.

Poor gastrointestinal function-poor motility**,** in addition to congenital anomalies producing polyhydraminos **(Kleigman, 2002)**, necrotizing enterocolitis, and other feeding disorders **(Rudolph&Hittner,1997; Golski&Rom, 2010).**

F) Metabolic-endocrine disorders:

Hypocalcemia, hypoglycemia, hyperglycemia, hypothermia, late metabolic acidosis and euthyroid but low T4 status**(Osborn et al., 2003; Shah&Sankaran, 2012).**

G) Renal disorders:

Immature renal function (including both filteration and tubular function), and electrolyte disturbance leading to hyponatremia, hypernatremia, hyperkalemia, renal tubular acidosis, renal glycosuria and edema **(Ramanathan&Sardesai, 2008; Hansen&Stoll, 2010).**

H) Infection:

Increased susceptibility to infection (congenital, prenatal, hospital acquired infection: bacterial, viral, fungal and protozoal **(Saigal, 2008)**, fetal growth restriction **(Eichenwald&Stark, 2008)**, behaviour and personality changes (**Saigal&Doyle, 2008).**

Etiology of preterm birth:

As the cause of labor still remains elusive, the exact cause of preterm birth is also unresolved.

Infact, the cause of 50% of preterm birth is never determined **(Simhan&Caritis, 2007; Thilo& Rosenberg, 2011).** Four different pathways have been identified that can result in preterm birth and have considerable evidence: precocious fetal endocrine activation, uterine over distension, decidual bleeding and intrauterine inflammation/infection. Activation of one or more of these pathways may happen over weeks even months **(Simhan&Caritis, 2007; Petrini et al., 2009).**

Causes can be categorized as follows:

A) Maternal background:

A number of factors have been identified that are linked to a higher risk of preterm birth:

1. Age at the upper and lower end of the reproductive years, be it more than 35 or less than 18 years of age **(Martius et al., 1998; Goldenberg et al., 2008).**
2. Pregnancy interval makes a difference as women with a 6 months span or less between pregnancies have a two-fold increase in preterm birth **(Conde-Agudelo, 2006).**
3. Stressful conditions and hard labor are probably linked to preterm birth **(Goldenberg et al., 2008;Salisbury &Wisner , 2011).**Women who have undergone previous surgically induced abortions have been shown to have a higher risk of preterm birth (less than 37 weeks) as well as extreme preterm birth (less than 25 weeks) **(Nicholas et al ., 2000).**
4. Adequate maternal nutrition is important, women with a low basal metabolic index are at increased risk of preterm birth, while obesity does not directly lead to preterm birth, however, it is associated with diabetes and hypertension which are risk factors by them selves **(Goldenberg et al., 2008).**