Doppler Cerebral Blood Flow Measurements, Serum Neuron-Specific Enolase and Neurodevelopmental Outcome in Early-Onset Neonatal Sepsis

Thesis

Submitted for partial fulfillment of MD degree in **Pediatrics**

Ву

Noha Mokhtar Kamal Mahmoud

M.B.B.Ch. (2007), M.Sc (2012) Faculty of Medicine, Ain Shams University

Under Supervision of

Professor/ Mohamed Sami El Shimi

Professor of Pediatrics Faculty of Medicine – Ain Shams University

Professor/ Nehal Mohamed El-Raggal

Professor of pediatrics Faculty of Medicine - Ain Shams University

Professor/ Hanan Mohamed Issa

Professor of Radiodiagnosis Faculty of Medicine – Ain Shams University

Doctor/ Rania Ali El-Farrash

Assistant Professor of Pediatrics Faculty of Medicine – Ain Shams University

Doctor/ Hebat Allah Ali Shaaban

Lecturer of Pediatrics
Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
2015

List of Contents

Subject Page No	
List of Abbreviations	i
List of Tablesv	V
List of Figuresis	K
Introduction	1
Aim of the Work5	5
Review of Literature	
Early Onset Neonatal Sepsis	5
Neonatal Brain Injury37	7
Neuron Specific Enolase Level in Brain Injury 48	3
Cranial Ultrasound and cerebral blood flow in Neonates	2
Neurodevelopment in Early Onset Neonatal Sepsis 61	1
Patients and Methods72	2
Results87	7
Discussion	
Conclusion	1
Recommendations	3
Summary	
References	
Arabic Summary	-

List of Abbreviations

Abbr. Full-term A.R.I.C.D : Association for Research in Infant and Child Development **AAP** : American Academy of Paediatrics **ACA** : Anterior cerebral artery AQ : Intelligence quotients of Q subscale **AUC** : Area under the ROC curve **BBB** : Blood-brain barrier BQ : Intelligence quotients of B subscale **BSID** : Bayley Scales of Infant Toddler Development **BSP** : Brain specific proteins \mathbf{BW} : Birth weight **CBC** : Complete blood count **CBF** : Cerebral blood flow **CBFV** : Cerebral blood flow velocity **CDC** : Centers for Disease Control and Prevention CI : Confidence interval CLD : Chronic lung disease cm/s : Centimeter/second **CNS** : Central nervous system **CoNS** : Coagulase negative staphylococci \mathbf{CQ} : Intelligence quotients of C subscale **CRP** : C reactive protein **CSF** : Cerebrospinal fluid \mathbf{CT} : Computed tomography **DAMP** : Damage-associated molecular pattern

List of Abbreviations (Cont.)

Abbr. Full-term DIC : Disseminated intravascular coagulation DO : Intelligence quotients of D subscale : Escherichia coli E. coli : End diastolic velocity, **EDV EEG** : Electroencephalographic **EGNN** : Egyptian Neonatal Network **EOS** : Early onset neonatal sepsis: EQ : Intelligence quotients of A subscale **FISH** : Fluorescence in situ hybridization : Gram **GBS** : Group B streptococcal **GMDS** : Griffiths mental development scale GO : General Intelligence Quotient \mathbf{GU} : Genitourinary **HPR** : Horseradish peroxidase Hs : Hours HSS : Hematologic scoring system I/T ratio : Immature to total neutrophil counts **IAP** : intrapartum antibiotic prophylaxis **ICA** : Internal carotid artery **ICH** : Intracranial haemorrhage **ICU** : Intensive care unit **IgM** : Immunoglobulin M IL : Interleukin

List of Abbreviations (Cont.)

Abbr.	Full-term
IQR	: Interquartile range
LP	: Lumbar puncture
LPS	: Lipopolysaccharide
LR-	: Negative likelihood ratio
LR+	: Positive likelihood ratio
Lt	: Left
MABP	: Mean arterial blood pressure
MAP	: Mean arterial blood pressure
MCA	: Middle cerebral artery
MRI	: Magnetic resonance imaging
MSOF	: Multiple system organ failure
n	: Number
NEC	: necrotizing enterocolitis
NICUs	: Neonatal intensive care units
NPP	: Negative predictive value
NSE	: Neuron-specific enolase
OFC	: Occipitofrontal circumference,
PAMP	: Pathogen-associated molecular pattern
PCR	: Polymerase chain reaction
PI	: Pulsatility index
PMNs	: Polymorpho neutrophils
PPV	: Positive predictive value
PROM	: Premature rupture of membranes
PRRs	: Pattern recognition receptors

List of Abbreviations (Cont.)

Abbr.	Full-term
PSV	: Peak systolic velocity
PT	: Prothrombin time,
PTT	: Partial thromboplastin time,
PV-	: Negative predictive value;
PV+	: Positive predictive value
PVL	: Periventricular leukomalacia
RI	: Resistive index
ROC	: Receiver-operating characteristic
ROM	: Rupture of Membranes
ROS	: Risk of sepsis
Rt	: Right
SAE	: Sepsis associated encephalopathy
SBIs	: Serious bacterial infections
SD	: Standard deviation,
SIRS	: Systemic inflammatory response syndrome
Std	: Standard deviation
SVD	: Spontaneous vaginal delivery
TLR	: Toll-like receptor
TMP	: TMB-Substrate solution
TNF-α	: Tumor necrosis factor-α
US	: Ultrasonography
UTI	: Urinary tract infection
VA	: Vertebral artery
VLBW	: Very low birth-weight infants
WBC	: White blood cell count

List of Tables

Table No.	Title Page No.				
Table (1):	Common bacterial agents causing neonatal sepsis in term infant				
Table (2):	Clinical findings in neonatal sepsis21				
Table (3):	Cerebrospinal fluid examination in high risk neonates without meningitis26				
Table (4):	Hematological scoring system used to diagnose neonatal sepsis				
Table (5):	Follner score; examination of clinical and hematological symptoms in neonatal septicemia				
Table (6):	Serum neuron-specific enolase results in neonates50				
Table (7):	Normal RI values in full term neonates during the first 24 hours of life				
Table (8):	Test sheet showing details of each scale 69				
Table (9):	Comparison of maternal characteristics between the studied groups				
Table (10):	Demographic and clinical characteristics in both study groups				
Table (11):	Diagnostic sepsis markers in sepsis group90				
Table (12):	Incidence of end-organ dysfunction/failure in both studied groups91				

List of Tables (Cont.)

Table No.	Title	Page	No.
Table (13):	Cerebral Doppler indices i studied groups		
Table (14):	Diagnostic performance of the Doppler indices using r operating characteristic (RO prediction of early onset sepsis	receiver- C) for	
Table (15):	Comparison between the area the ROC curves associated various cerebral Doppler indepredictors of early onset sepsis.	d with lices as	
Table (16):	Baseline Neurone-specific (NSE) level in both studied grow		
Table (17):	Neuron specific enolase (NSE) complicated sepsis group (n=16		
Table (18):	Neuron specific enolase (NSE) sepsis-group with and encephalopathy	without	
Table (19):	Diagnostic performance of neuron-specific enolase Receiver-operating chara (ROC) for prediction of earl sepsis	using cteristic y onset	
Table (20):	Outcome measures in both groups		

List of Tables (Cont.)

Table No.	Title	Page No.
Table (21):	Griffiths mental developmental 3 months in both studied groups	
Table (22):	Griffiths mental developmental 6 months in both studied groups	
Table (23):	Griffiths mental developmental 3 and 6 months in sepsis group .	
Table (24):	Correlation between baseline n specific enolase and cerebral l indices in the whole studied pop and in infants with or without se	Doppler pulation
Table (25):	Correlation between baseline in specific enolase and the Comental developmental scale months in the whole study population infants with or without see	Griffiths at 3 pulation
Table (26):	Correlation between baseline n specific enolase and the C mental developmental scale months in the whole study pop and in infants with or without se	Griffiths at 6 pulation
Table (27):	Correlation between Doppler and the Griffiths mental develop scale at 3 months in the whol population	pmental e study

List of Tables (Cont.)

Table No.	Title	Page No.
Table (28):	Correlation between the cerebral E indices and the Griffiths developmental scale at 6 months whole studied population	mental in the
Table (29):	Correlation between the composition between the composition indices and the Grand mental developmental scale months in the non-sepsis group	riffiths at 3
Table (30):	Correlation between the D indices and the Griffith developmental scale at 6 months non-sepsis group	mental in the
Table (31):	Correlation between the correlation between the correlation between the correlation and the Grand mental developmental scale months in the sepsis group	riffiths at 3
Table (32):	Correlation between the D indices and the Griffiths developmental scale at 6 months sepsis group	mental in the

List of Figures

Figure No.	Title Page	No.
Figure (1):	Incidence of early-and late-onset invasive group B streptococcal (GBS) disease	10
Figure (2):	Factors influencing the balance between health and disease in neonates exposed to a potential pathogen	16
Figure (3):	Inflammation in the developing brain	43
Figure (4):	Cerebral blood flow velocity tracing obtained at the anterior fontanelle from the anterior cerebral artery	55
Figure (5):	Normal Doppler images and spectral waveforms	
Figure (6):	Flow velocities in cerebral arteries in postnatal days	57
Figure (7):	Volume of cerebral blood flow in relation to postmenstrual age	58
Figure (8):	The kit and the carrying case of Griffiths mental developmental scale	66
Figure (9):	ACA and MCA RI in both study groups	93
Figure (10):	ACA and MCA PSV in both study groups	
Figure (11):	ACA and MCA EDV in both study groups.	

List of Figures (Cont.)

Figure No.	Title Pag	е	No.
Figure (12):	Receiver-operating characteristic (RO curve for prediction of sepsis using t ACA RI.	he	
Figure (13):	Receiver-operating characteristic (RO curve for prediction of sepsis using the ACA PSV	he	
Figure (14):	Receiver-operating characteristic (RO curve for prediction of sepsis using t ACA EDV	he	
Figure (15):	Receiver-operating characteristic (RO curve for prediction of sepsis using t MCA RI.	he	
Figure (16):	Receiver-operating characteristic (RO curve for prediction of sepsis using t MCA PSV	he	
Figure (17):	Receiver-operating characteristic (RO curve for prediction of sepsis using t MCA EDV.	he	
Figure (18):	Comparison of the receiver-operation characteristic (ROC) curves prediction of sepsis using various AC and MCA Doppler indices	for CA	
Figure (19):	Box plot showing baseline neuron specific enolase in both study groups	ne-	

List	Ωf	Fiai	ıres

Figure (20):	Neuron specific enolase (NSE) level in complicated sepsis group				
	List of Figures (Cont.)				
Figure No.	Title Page No	ο.			
Figure (21):	Receiver-operating characteristic (ROC) curve for prediction of early onset sepsis using the baseline neurone-specific enolase level	05			
Figure (22):	Griffith mental developmental scale at 3 months in both studied groups	28			
Figure (23):	Griffiths mental developmental scale at 6 months in both study groups	10			
Figure (24):	Griffiths mental developmental scale's GQ at 3 and 6 months in both studied groups	11			
Figure (25):	Griffiths mental developmental scale's AQ at 3 and 6 months in both studied groups	12			
Figure (26):	Griffiths mental developmental scale's BQ at 3 and 6 months in both studied groups				
Figure (27):	Griffiths mental developmental scale's CQ at 3 and 6 months in both studied groups	14			
Figure (28):	Griffiths mental developmental scale's DQ at 3 and 6 months in both studied				

groups......115

List	οf	Fiai	ires

Figure (29):	Griffiths mental developmental scale's
	EQ at 3 and 6 months in both studied
	groups116



سورة البقرة الآية: ٣٢