



Neuron-specific Enolase, Serum100 B, Electroencephalography as Indicators of Extent of Brain Damage in Post Cardiac Arrest Patients

Thesis

*Submitted for Partial Fulfillment of
Master Degree in **Pediatrics***

By

Sondos Ahmed Salaheldin Ahmed

M.B.B.CH

Faculty of Medicine - Ain Shams University (2013)

Under Supervision of

Prof. Dr. Magda Yehia Hussien El-Seify

Professor of Pediatrics

Faculty of Medicine, Ain Shams University

Dr. Ahmed Rezk Ahmed

Lecturer of Pediatrics

Faculty of Medicine, Ain Shams University

Dr. Mennatullah Osama Shattah

Lecturer of Pediatrics

Faculty of Medicine, Ain Shams University

Faculty of Medicine, Ain Shams University

2018

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

سورة البقرة الآية: ٣٢

Acknowledgments

*First and foremost, I feel always indebted to **Allah** the Most Beneficent and Merciful.*

*I wish to express my deepest thanks, gratitude and appreciation to **Prof. Dr. Magda Yehia Hussien Elseify**, Professor of Pediatrics, Faculty of Medicine, Ain Shams University, for her meticulous supervision, kind guidance, valuable instructions and generous help.*

*Special thanks are due to **Dr. Ahmed Rezk Ahmed**, Lecturer of Pediatrics, Faculty of Medicine, Ainshams University, for his sincere efforts, fruitful encouragement.*

*I am deeply thankful to **Dr. Menatallah Osama Shatta**, Lecturer of Pediatrics, Faculty of Medicine, Ainshams University, for her great help, outstanding support, active participation and guidance.*

I dedicate this work to the memory of my beloved mother, for whom I owe all blessings in my life.

To my father, my sisters for their continuous support, care and love.

Sondos Ahmed Salaheldin



To:

My parents

*for their endless love, support,
and continuous care*

&

My Family



List of Contents

Title	Page No.
List of Tables	6
List of Figures	8
List of Abbreviations.....	10
Introduction.....	- 1 -
Aim of the Work	4
Review of Literature	
▪ Cardiac Arrest and Post Cardiac Arrest Syndrome	5
▪ Post Cardiac Arrest Brain Injury	25
▪ Prognosis of Hypoxic Ischemic Brain Injury	35
Patients and Methods	44
Results	58
Discussion.....	90
Summary	106
Conclusion	113
Recommendations	114
References	115
Arabic Summary	

List of Tables

Table No.	Title	Page No.
Table (1):	Descriptive data of the study group:.....	58
Table (2):	Age stratification of the study group:	59
Table (3):	Originally affected systems in patients of the study group:.....	62
Table (4):	Circumstances of cardiac arrest (cause, duration), mortality convulsions, sepsis, ventilation and cardiac supports before and after cardiac arrest:	63
Table (5):	Routine laboratory investigations of the study group:	65
Table (6):	Serum Neuron-specific enolase, Serum100B, EEG recording results in the study group:	66
Table (7):	ICU admission duration, survival, survival duration after arrest:.....	68
Table (8):	Survival percentage in different age groups:	69
Table (9):	Relation between presence of sepsis and mortality:	69
Table (10):	Relation between presence of convulsions and mortality:	69
Table (11):	Relation between biomarkers, EEG and outcome of the studied group of patients:.....	70
Table (12):	Relation between Neuron-specific enolase, Serum100B, EEG and mortality:.....	73
Table (13):	Relation between ICU admission duration and survival:	74
Table (14):	Correlation between Neuron-specific enolase, Serum100 B and duration of arrest:.....	74
Table (15):	Relation between EEG findings and duration of arrest:.....	76

List of Tables *cont...*

Table No.	Title	Page No.
Table (16):	Comparison between patients with cardiac arrest less than 7 minutes and those with more than 7 minutes as regard biomarkers levels and EEG:	77
Table (17):	Relation between serum biomarkers, EEG findings and cause of arrest:	80
Table (18):	Relation between serum biomarkers, EEG findings and the presence of convulsions:	81
Table (19):	Relation between Neuron-specific enolase levels and EEG findings:.....	82
Table (20):	Relation between Serum 100B levels and EEG findings:	83
Table (21):	Correlation between serum Neuron-specific enolase and Serum 100B levels:	84
Table (22):	Correlation between Neuron-specific enolase, Serum 100B and Survival duration after arrest:.....	84
Table (23):	Relation between EEG findings and Survival duration after arrest:.....	85
Table (24):	Relation between biomarkers, EEG findings and ICU admission duration more or less than 12 days:.....	86
Table (25):	Kaplan Mayer analysis for the relation between the studied biomarkers, EEG findings and overall survival:	87
Table (26):	Relation between patients' original system affection and survival duration after arrest:.....	89

List of Figures

Fig. No.	Title	Page No.
Figure (1):	Ischemia-reperfusion stages	10
Figure (2):	Pathophysiology of cardiac arrest	10
Figure (3):	Clinical manifestations of cardiac arrest	12
Figure (4):	Pittsburgh Cardiac arrest categories	14
Figure (5):	Sequence of actions in cardiopulmonary resuscitation	15
Figure (6):	Phase of post-cardiac arrest syndrome	27
Figure (7):	EEG equipment.....	51
Figure (8):	Electrode placement.....	52
Figure (9):	Measurement of Cz	53
Figure (10):	Measurements of T3, C3, Cz, C4, T4.....	54
Figure (11):	Measurements of Fpz, Fz, Cz, Pz, Oz.....	55
Figure (12):	Measurements of Fp1, F7, T3, T5, O1, Oz	55
Figure (13):	Measurement of F3,F4	56
Figure (14):	Age stratification of the study group:.....	59
Figure (15):	Gender distribution of the study group.....	60
Figure (16):	Order of birth distribution of the study group:	60
Figure (17):	Parental consanguinity in the study group:.....	61
Figure (18):	Originally affected systems of patients of the study group.	62
Figure (19):	Cause of arrest in the study group:	64
Figure (20):	Mortality in the study group:.....	64

List of Figures *cont...*

Fig. No.	Title	Page No.
Figure (21):	EEG findings in the study group:.....	67
Figure (22):	Survival percentage among the study group:	68
Figure (23):	Relation between EEG recording results and mortality in the studied group.	72
Figure (24):	Correlation between Neuron-specific enolase and duration of arrest:.....	75
Figure (25):	Neuron-specific enolase level in patients with duration of arrest more or less than 7 minutes:	78
Figure (26):	Receiver operating characteristic curve (ROC) for Sensitivity and specificity of Neuron-specific enolase in prediction of duration of arrest more or less than 7 minutes	79
Figure (27):	Relation between EEG findings and survival duration after arrest:.....	88

List of Abbreviations

Abb.	Full term
<i>CPR</i>	<i>Cardiopulmonary resuscitation</i>
<i>EEG</i>	<i>Electroencephalogram</i>
<i>ICU</i>	<i>Intensive care unit</i>
<i>IHCA</i>	<i>In hospital cardiac arrest</i>
<i>NSE</i>	<i>Neuron-specific enolase</i>
<i>OHCA</i>	<i>Out hospital cardiac arrest</i>
<i>ROSC</i>	<i>Return of spontaneous circulation</i>
<i>S100B</i>	<i>Serum100B</i>

Introduction

Post cardiac arrest syndrome occurs after return of spontaneous circulation (ROSC) following cardiorespiratory arrest. It reflects a state of whole-body ischemia and subsequent reperfusion. It is often super-imposed on the underlying condition, which caused the cardiac arrest, the pre-existing comorbidities, and other complications of resuscitation. Its severity depends on the duration, cause of cardiac arrest and the quality of resuscitation process (*Binks et al., 2010*).

Post cardiac arrest syndrome is a unique and complex combination of pathophysiological processes, including post-cardiac arrest brain injury, post-cardiac arrest myocardial dysfunction, systemic ischemia /reperfusion response and the unresolved pathological process that caused the cardiac arrest (*Neumar et al., 2008*).

Cardiac arrest causes a primary and secondary brain injury. The primary injury occurs at the time of arrest and is non-reversible, and the secondary injury follows return of spontaneous circulation (ROSC) and subsequent cerebral reperfusion and is potentially reversible (*Temple et al., 2012*).

The brain is exquisitely sensitive to hypoxia. Within 20 seconds of circulatory arrest, neuronal oxygen stores are used up leading to unconsciousness. After 5 minutes, glucose and

adenosine triphosphate (ATP) stores are depleted. This leads to disruption in calcium homeostasis, free radical formation, and the activation of harmful protease cascades and cell death signaling mechanisms. This causes the primary cerebral injury (*Temple et al., 2012*).

After restoration of cerebral blood flow, ATP is regenerated which leads to devastating free radical formation and the secondary cerebral injury. Cell death continues by both apoptosis and necrosis (*Temple et al., 2012*).

Cardiac arrest is a devastating event; overall survival from out-of-hospital cardiac arrest is 6.4% (children 9.1%, adolescents 8.9%, and infants 3.3%) Survival rates for in-hospital cardiac arrest ranged from 16 to 38% in different studies published in the last decade (*Manole et al., 2009*).

Brain injury was the cause of death in 68% after out-of-hospital cardiac arrest and in 23% after in-hospital cardiac arrest. The unique vulnerability of the brain is attributed to its limited tolerance of ischemia as well as its unique response to reperfusion (*Neumar et al., 2008*).

Serum brain-specific biomarkers e.g. Neuron-specific enolase (NSE) and serum 100B (S100B) have the potential to assist in the early detection and quantification of the severity of brain injury, response to therapeutic interventions, and prediction of outcome after cardiac arrest (*Fink et al., 2014*).

The rationale of dosing markers of neuronal injury in the blood of resuscitated patients is that higher levels of biomarkers correlate with a higher extent of brain damage and consequently lower chances of recovery (**Sandroni et al., 2015**).

S100B is secreted by astrocytes or can spill from injured cells and enter the extracellular space or bloodstream. Serum levels of S100B increase in patients during the acute phase of brain damage (**Michetti et al., 2018**).

Electroencephalography has been studied extensively as a tool for evaluating the depth of coma and extent of damage after cardiac arrest. Many malignant EEG patterns have been associated with poor functional outcome, the most reliable of which appear to be generalized suppression to $<20\mu\text{V}$, burst-suppression pattern with generalized epileptiform activity, and generalized periodic complexes on a flat background (**Neumar et al., 2008**).

Aim of the Work

To study the levels of Neuron-specific enolase, Serum 100B, Electroencephalogram patterns in post cardiac arrest pediatric patients and to correlate these findings with cardiac arrest circumstances and patients' outcome.

Chapter 1

Cardiac Arrest and Post Cardiac Arrest Syndrome

Definition:

Cardiac arrest is one of the greatest medical emergencies. It is characterized by absent or inadequate cardiac contraction resulting in circulatory failure. Unless cardiac arrest is quickly corrected by resuscitation techniques, it is fatal (*Stoppler et al., 2016*).

Advancement in resuscitation techniques has resulted in development of new disease entity termed 'Post cardiac arrest syndrome'. A term that was first used by Vladimir Negovsky in the 1960s (*Geocadin et al., 2008*).

Post cardiac arrest syndrome is defined as a unique and complex combination of pathophysiological processes resulting from Cardiac arrest, it is composed of:

1. Post cardiac arrest brain injury,
2. Post cardiac arrest myocardial dysfunction,
3. Systemic ischemia /reperfusion response,
4. The unresolved pathological process that caused the cardiac arrest (*Geocadin et al., 2008*).