STUDY OF SERUM INTERLEUKIN-6 AS A PREDICTOR OF NEONATAL SEPSIS IN NEWBORNS WITH SUSPICION OF INFECTION

Thesis

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By

Hala Mohamed Ismail Osman

M.B.B.,Ch

Supervised By

Professor Dr. Mohamed Ahmed Abo Elhassan

Professor of Pediatrics

Faculty of Medicine – Cairo University

Professor Dr. Sahar Abd Elatty Sharaf

Professor of Clinical and Chemical Pathology

Faculty of Medicine – Cairo University

Dr. Walaa Sharaany Abd El Hamid

Lecturer of Pediatrics

Faculty of Medicine – Cairo University

Faculty of Medicine

Cairo University

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بسم الله الرحمن الرحيم
إقرأ باسم ربك الذي
خلق{1}خلق الإنسان
من علق{2} إقرأ وربك
الأكرم{3}الذي علم
بالقلم{4}علم الإنسان ما
لم يعلم{5}
صدق الله العظيم
سورة العلق
الآيات (1-5)

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Hala Mohamed

LIST OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbrev.	Full term
AA	: Amino acid
AP-1	: Activator protein 1
APPs	: Antimicrobial proteins and peptides
bLF	: Bovine Lactoferrin
C/EBPbeta	: CAAT/enhancer-binding protein beta
CNS	: Central nervous system
CoNS	: Coagulase negative Staphylococci
CRP	: C- reactive protein
CSF	: Cerebrospinal fluid
CVC	: Central venous catheter
DIC	: Disseminated intravascular coagulation
E- coli	: Escherichia coli
ELISA	: Enzyme-Linked Immunosorbent Assay
EOS	: Early onset sepsis
ERK	: Extracellular signal–regulated kinase
FFP	: Fresh frozen plasma
GA	: Gestational age
GBS	: Group B streptococci
G-CSF	: Granulocyte colony stimulating factor
GI	: Gastrointestinal
GM-CSF	: Granulocyte-macrophage colony stimulating factor
gp 130	: Glycoprotein 130
HB	: Haemoglobin
HCMV	: Human cytomegalovirus
I:T ratio	: Immature to total neutrophil ratio
Ig	: Immunoglobulin
IgA	: Immunoglobulin A
IgG	: Immunoglobulin G
IgM	: Immunoglobulin M
IL-1 RA	: Interleukin-1 receptor antagonist
IL-1	: Interleukin-1
IL-11	: Interleukin-11
Il-6 R	: Interleukin-6 receptor
IL-6	: Interleukin-6
IL-8	: Interleukin-8

LIST OF ABBREVIATIONS (Cont...)

Abbrev.	Full term
INF-γ	: Interferon-gamma
IV	: Intravenous
IVIG	: Intravenous immunoglobulins
JAK	: Janus Kinase
kDa	: KiloDalton
LBW	: Low birth weight
LOS	: Late onset sepsis
MAPK	: Mitogen-activated protein kinase
mIL-6R	: Membrane-bound interleukin-6 receptor
MPV	: Mean platelet volume
MRSA	: Methicillin Resistant Staphylococcus Aureus
NEC	: Necrotizing enterocolitis
NICU	: Neonatal intensive care unit
NK	: Natural killer cells
PCR	: Polymerase chain reaction
PDW	: Platelet distribution width
PLT	: Platelets
PMN	: Polymorphonuclear
PPHN	: Persistent pulmonary hypertension of the newborn
PROM	: Premature rupture of membranes
PT	: Prothrombin time
PTT	: Partial thromboplastin time
RDS	: Respiratory distress syndrome
SHP-2	: *Src* homology 2–containing tyrosine phosphatase
sIL-6R	: Soluble form of interleukin-6 receptor
SIRS	: Systemic inflammatory response syndrome
SOCS	: Suppressors of cytokine signaling
Staph. aureus	: Staphylococcus aureus
STAT	: Signal transducers and activator of transcription
TF	: Transcription factor
Th17	: Type 17 helper cells
Th2	: Type 2 helper cells.
TLC	: Total leucocytic count

LIST OF ABBREVIATIONS (Cont...)

Abbrev.	Full term
TNF	: Tumor necrosis factor
TNF-α	: Tumor Necrosis Factor-alpha.
TPN	: Total parentral nutrition
UTI	: Urinary tract infection
VLBW	: Very low birth weight
WBC	: White blood cells

Study of serum interleukin-6 in newborns with suspicion of infection

Abstract

Key words:(Interleukin-6, Neonatal sepsis,Cytokines)

Introduction: Sepsis is a significant cause of morbidity and mortality in the newborn, particularly in preterm, low birth weight infants. Despite advances in neonatal care, infections remain common and sometimes life-threatening in neonates admitted to the neonatal intensive care unit (NICU). Interleukin-6 belongs to the family of cytokines. It is one of the mediators of inflammation that are released early in the course of septic shock and is crucial in initiating the immune response.

Objective: The purpose of study was to evaluate the role of serum interleukin-6 as an early diagnostic marker in early and late onset neonatal sepsis. **Subjects and methods:** This is a cross sectional study conducted on 88 neonates with suspicion of infection. Newborns were classified as a confirmed, probable or no infection, based on the results of cultures, chest X-rays, laboratory data and clinical signs. Grouping was done prior to measuring levels of interleukin-6.**Results:** The proven sepsis group contained 23 neonates, the probable sepsis 33 neonates and not infected 32 neonates.Interleukin-6 was found to be statistically higher in the sepsis groups (proven and probable sepsis) than the non infected group. **Conclusion:** Interleukin-6 proved to be of benefit in discriminating infected neonates from non infected ones.

INTRODUCTION

Sepsis is a significant cause of morbidity and mortality in the newborn, particularly in preterm, low birth weight infants, despite advances in neonatal care, infections remain common and sometimes life-threatening in neonates admitted to the neonatal intensive care unit (NICU) ***(Stoll et al., 2011).***

Despite extensive investigation, no single test meets the criteria that would make it an ideal marker for early diagnosis of sepsis in the newborn. Generally, screening includes a complete blood count with differential and may be accompanied by other adjuvant tests such as a C-reactive protein (CRP) ***(Kayange et al., 2010).***

Screening tests, including white blood cell count and acute phase reactants, such as C-reactive protein (CRP), have poor positive predictive values in septic neonates: 40% in symptomatic neonates and as low as 1% to 2% in asymptomatic neonates ***(Terrin et al., 2011).***

Neonatal blood culture positive rates have been found to range from 25-54% ***(Kayange et al., 2010).***

Interleukin-6 belongs to the family of cytokines. It is one of the mediators of inflammation that are released early in the course of septic shock and is crucial in initiating the immune response, as well as the activation of T lymphocytes and B lymphocytes and lymphocytes proliferation and differentiation. In addition, interleukin-6 is a potent pyrogen. It also induces the release of acute phase proteins like C-reactive protein (CRP) ***(Tamayo et al., 2011).***

Interleukin-6 reaches its peak after 2 hours of bacterial stimulus onset, so that its level may be elevated before the start of the symptoms and before the rise of routinely used markers ***(Campos et al., 2010).*** IL-6 was reported to appear earlier in plasma than CRP ***(Tess et al., 2011).***

AIM OF THE WORK

The purpose of this prospective study was to evaluate the role of serum interleukin-6 as an early diagnostic marker in early and late onset neonatal sepsis.

NEONATAL SEPSIS

Definition:

Neonatal sepsis or septicemia is a clinical syndrome characterized by systemic signs of circulatory compromise (e.g., poor peripheral perfusion, pallor, hypotonia, poor responsiveness) caused by invasion of the bloodstream by pathogenic microorganisms in the first month of life. In the pre-antibiotic era neonatal sepsis was usually fatal ***(Edmond and Zaidi, 2010).***

The term systemic inflammatory response syndrome (SIRS) is most frequently used to describe this unique process of neonatal infection and the subsequent systemic response .Neonates with SIRS have a spectrum with clinical symptoms that represent progressive stages of the pathologic process ***(Wynn et al., 2010).***

Incidence:

The incidence of neonatal sepsis varies among the different geographic areas, the highest being registered in Africa and Asia (23-38/1,000 live births) and the lowest, in countries such as the U.S. and Australia (range, 1.5-3.5 /1,000 live births). In South America and the Caribbean, the incidence of neonatal sepsis ranges between 3.5 and 8.9/1,000 live births, while in Mexico, the reported rates range between 4 and 15.4/1,000 live births ***(Leal et al., 2012).***

Another study done showed that the rate of early onset neonatal sepsis was 0.98 per 1000 live births. Range across centers (0.33 to 2,44 cases per 1000 live births),Incidence is

highest among infants with a birth weight of 401 to 1500 g and lowest among those with birth weight more than 2500g ***(Stoll et al., 2011)*.**

Mode of infection:

1) Prenatal infection:

Throughout pregnancy and until the membranes rupture, the fetus is relatively protected from the microbial flora of the mother by the chorioamniotic membranes, the placenta and the antibacterial factors in amniotic fluid, however, there are many ways that infectious agents can reach the fetus to cause infection. Some microbial species cause intrauterine infections that present as congenital infections in the newborn ***(Polin, 2012)*.**

2) Natal infection:

The human birth canal is colonized with aerobic and anaerobic organisms. Vaginal delivery inevitably results in contamination and the beginning of colonization of skin and gut of the newborn. The commonest causative organisms are Group B Streptococci (GBS), gram-negative enteric organism, Staphylococcus aureus and Streptococcus fecalis ***(Stoll et al., 2011)*.**

3) Postnatal infection:

It occurs in the delivery room or the newborn nursery via respiratory tract, gastrointestinal tract, umbilical stump, infected circumcision wound. These infections may be transmitted through: