Synthetic and Excretory Hepatic Dysfunction in Gram-negative Bacteremia in Premature Neonates

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By

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ABSTRACT

INTRODUCTION: Sepsis is frequent and serious cause of liver dysfunction in neonates, neonatal sepsis induces synthetic liver dysfunction and coagulation abnormalities that may be indicators of sepsis before blood culture results. **OBJECTIVE:** This work aims to detect execretory and synthetic hepatic dysfunction in preterm neonates with positive blood culture to study the effect of sepsis on liver functions and compare between gram positive and gram negative pathogens causing sepsis regarding effect on liver functions and outcome. **SUBJECT AND METHODS:** Our study included 100 preterm neonates who were divided in two groups: Group I, included 50 neonates who had positive blood culture results and group II, included 50 preterm neonates in whom all risk factors of sepsis were excluded by history, examination and laboratory investigations. Blood samples were taken from all neonates to measure; ALT, AST, ALP, GGT, TSB, DSB, TP. Albumin, PT, APTT and glucose levels. **RESULTS**: In our study we found that Klebsiella was the most common organism isolated from cases with positive blood culture, 21 out of 50 (42% of all septic neonates and 63.6% of neonates with gram negative bacteremia). In this study we found that 21.2% of neonates with gram negative bacteremia had abnormal ALT, 48.5% had abnormal AST, 87.9% had abnormal ALP and 97% had abnormal GGT levels while 5.9% of gram positive cases had abnormal ALT, 64.7% had abnormal AST, 70.6% had abnormal ALP and all cases had abnormal GGT levels. **CONCLUSION**: Gram negative bacteria more common than gram positive and Klebsiella is the most common isolated organism. Liver enzymes abnormalities are more common in preterm neonates with gram negative sepsis. Mortality rate among septic cases was 62%.

Key words: ▪ Preterm ▪Neonatal sepsis ▪Hepatic dysfunction

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Dedication

To my Father and my Mother who taught me the principles and patience

To all my professors and colleagues

Mohammed Salah

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Abbreviations

5'NT	5' nucleotidase
AP	Alkaline phosphatase
ALT	Alanine aminotransferase
AAOG	American Academy of Obstetrics and Gynecology
AAP	American Academy of Pediatrics
APTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
BSEP	Bile salt export pump
BMPs	Bone morphogenetic proteins
BUN	Blood urea nitrogen
CDC	Centers for Disease Control and Prevention
CDCT	Chenodeoxycholyl taurine
CT	Choly taurine
CNS	Central nervous system
CF	Complement fixation
CONS	Coagulase negative staphylococcus aureus
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CMV	Cytomegalovirus
DIC	Disseminated intravascular coagulation
DNA	Deoxy-ribonucleic acid
EOS	Early onset sepsis
LOS	Late onset sepsis
ELBW	Extreme low birth weight

ELISA	Enzyme-linked Immunosorbent assay
ESR	Erythrocyte sedimentation rate
FDPs	Fibrin Degradation Products
FGFs	Fibroblast growth factors
FFP	Fresh frozen plasma
G6PD	Glucose-6-phosphate dehydrogenase
GALT	Galactose-1-phosphate uridyltransferase
GBS	Group B streptococcal sepsis
GGT	Gamma glutamyl transferase
HI	Hemagglutination inhibition
HAV	Hepatitis A virus
HSV	Herpes simplex virus
HIV	Human immunodeficiency virus
IFA	Immunofluorescent assay
IL6	Interleukin 6
INR	International normalized ratio
KCs	Kupffer cells
LA	Latex agglutination
LPS	Lipopolysaccharide
MBC	Minimum bactericidal concentration
MIC	Minimum inhibitory concentration
MDR-3	Multidrug-resistant protein 3
MODS	Multiple organ dysfunction syndrome
NASPGHAN	North American Society for Pediatric Gastro-enterology, Hepatology, and Nutrition
NEC	Necrotizing enterocolitis

NH	Neonatal haemochromatosis
NICU	Neonatal intensive care unit
NO	Nitric oxide
PN	Parenteral nutrition
PNALD	Parenteral nutrition-associated liver disease
PCO2	Partial pressure of carbon dioxide
PCR	Polymerase chain reaction
PH	Minus log of hydrogen ion concentration
PO2	Partial pressure of oxygen
PROM	Premature rupture of membranes
PFIC	Progressive familial intrahepatic cholestasis
PT	Prothrombin time
PROWESS	Recombinant Protein C Worldwide Evaluation in Severe Sepsis
RBCs	Red blood cells
RES	Reticuloendothelial system
RNA	Ribo Nucleic Acid
NTCP	Sodium-dependent taurocholate cotransporter
SIRS	Systemic inflammatory response syndrome
TORCH	Toxoplasmosis, Other, Rubella virus, Cytomegalovirus (CMV), and Herpes Simplex Virus (HSV)
TP	Total Protein
TPN	Total parenteral nutrition
TNF-Q	Tumor necrosis factor alpha
UDPGT	Uridine diphosphoglucuronyl transferase
VZV	Varicella-zoster virus

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Introduction

Neonatal sepsis remains an important cause of morbidity and mortality in newborns (**Beak et al., 2003**).

The microorganisms most commonly associated with early-onset infection include group B Streptococcus (GBS), Escherichia coli, Haemophilus influenzae, and Listeria monocytogenes. Organisms that have been implicated in causing late-onset sepsis syndrome include Coagulase-negative staphylococci, Staphylococcus aureus, E coli, Klebsiella, Pseudomonas, Enterobacter, Candida, GBS, Serratia, Acinetobacter, and Anaerobes (**Fanaroff et al., 2006).**

Severe infection or sepsis is almost associated with activation of coagulation system setting up a vicious circle (**Leviton et al., 2004**). Sepsis is the most common cause of disseminated intravascular coagulation and closely linked to the development of multiple organ dysfunction syndromes (**Aird et al., 2003**).

Hyperbilirubinemia and liver enzyme abnormalities are commonly observed in sepsis (**Shamir et al., 2000**). Sepsis is frequently associated with cholestasis specifically Gram-negative sepsis due to endotoxin-induced inhibition of bile salt transport (**Trauner et al., 2003**).

Nisha et al. (2006) observed that most cases of sepsis associated with cholestatic jaundice had evidence of gram-negative bacteremia, with Escherichia coli the most common pathogen.

Liver enzymes abnormalities in neonates in the series of **Shamir et al. (2000)** accompanied 46.3%of gram-negative bacteremia and 12.9% of

coagulase negative staphylococcal bacteremia and were more common than elevated conjugated bilirubin. Mean while infants with gram-negative bacteremia and elevated liver enzymes who were not fed for a longer period compared to infants with gram-negative bacteremia with normal liver enzymes showed significant conjugated hyperbilirubinemia. In the same study klebsiella pneumoniae sepsis was significantly associated with elevated liver enzymes compared to other gram-negative organisms.

Preterm infants are at special risk of hepatic decompensation because their immaturity results in a delay in achieving normal detoxification and synthetic function **(Beath, 2003).**

Aim of the Work

Our study aims to:

- Detect execretory and synthetic hepatic dysfunction in preterm neonates with positive blood culture to study the effect of sepsis on liver functions.
- Compare between gram positive and gram negative pathogens causing sepsis regarding:
    a. Effect on liver functions
    b. Outcome and prognosis