Study of Neutrophil functions in infants and children with Recurrent Infections

Thesis

Submitted for partial fulfillment of Master degree in Pediatrics

By

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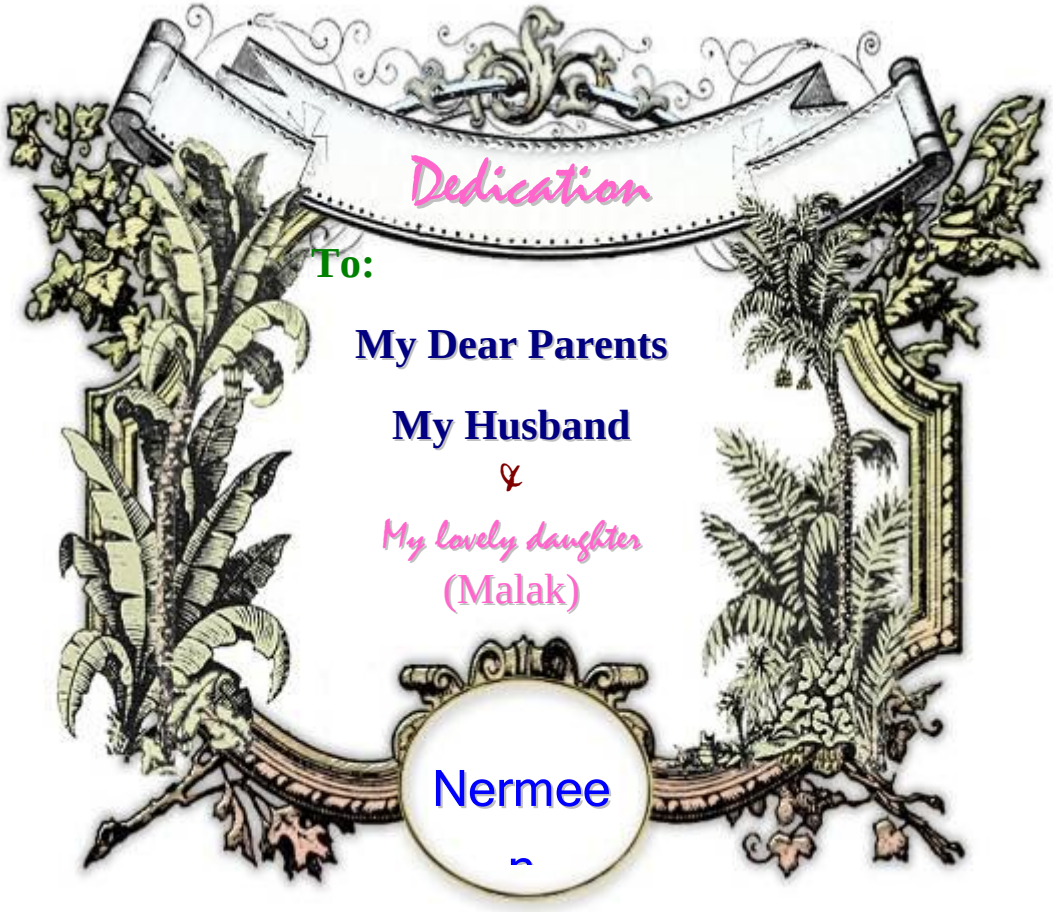
بسم الله الرحمن الرحيم
وَأَنْزَلَ اللهُ عَلَيْكَ
الكِتَابَ والحِكْمَةَ
وَعَلَّمَكَ مَا لَمْ
تَكُنْ تَعْلَمُ
وَكَانَ فَضْلُ اللهِ
عَلَيْكَ عَظِيمًا
صدق الله العظيم
آية (١١٣) سورة النساء


Dedication
To:
My Dear Parents
My Husband
&
My lovely daughter
(Malak)
Nermee
n

Acknowledgment

First and above all, I pray thanking **Allah** *for His blessing and granting me the effort to complete and achieve this work.*

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Last, but not least, I would like to thank the patients and their parents who accepted to participate in the study. May Allah grant them full recovery.

Nermeen Shawky

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List of Abbreviations

Abb.	Full term
AD	Autosomal dominant
AR	Autosomal recessive
AT	Ataxia telangiecatsia
BCG	Bacillus calmette-guerin
CD	Clusters of differentiation
CFU-G	Colony forming unit granulocyte
CFU-GMP	Colony forming unit granulocyte macrophage progenitor
CGD	Chronic granulomatous disease
CHS	Chediak Higashi syndrome
DHR	Dihydrorhodamine test
FTT	Failure to thrive
G6Pase	Glucose 6 phosphatase
G6PD	Glucose 6 phosphate dehydrogenase
G-CSF	Granulocyte colony stimulating factor
GM-CSF	Granulocyte macrophage colony stimulating factor
Gp	Glycoprotein
GSD	Glycogen storage disease
H_2O_2	Hydrogen peroxide
HIES	Hyper immunoglobulin E syndrome
HLH	Hemophagocytic lymphohisticytosis
IgA	Immunoglobulin A
IDR	Immunodeficiency disease related score
IL	Interleukin
LAD	Leucocyte adhesion defect
LPS	Lipopolysaccharide

List of Abbreviations (Cont...)

Abb.	Full term
MPO	Myeloperoxidase
NADPH	Nicotinamide adenine dinucleotide phosphate oxidase enzyme
NBT	Nitro blue tetrazoluim test
NETs	Neutrophil extracellular traps
NK	Natural killer
O_2^-	Superoxide
OH	Hydroxyl radical
PHOX	Phagocyte oxidase enzyme
PID	Primary immunodeficiency
PMA	Phorbol methyl acetate
PMNs	Polymorphonuclear leucocytes
PMP	Pathogen-associted molecular pattern
PRR	Pattern recognition receptors
RAC 2	Ras related C3 botulinuim toxin
ROS	Reactive oxygen species
S. Aureus	Staphylococcal aureus
SCID	Severe combined immunodeficiency
SI	Stimulation index
SIgAD	Selective IgA deficiency
SOD	Superoxide dismutase
TMP-SMX	Trimethoprim-sulfamethoxazole
TNF-α	Tumor necrosis factor-α
WAS	Wiskott Aldrich syndrome

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Introduction

Neutrophils are the first line of defense against bacterial invasion. As such, primary alterations in their number and function can result in propensity for serious, often life threatening infections. In general, patients with neutrophil dysfunction present with chronic, deep tissue infections rather than with overt sepsis, which is more likely to occur after a deep infection has gone unrecognized or improperly treated for a few days or weeks ***(Kyono and Coates, 2002)***.

Although practice parameters have been published recently for the diagnosis of wide range of primary immunodeficiency diseases, including phagocyte defects, few tests are widely available for specific evaluation of phagocyte function ***(Bonilla et al., 2005).*** The most important step in the diagnosis of a functional disorder of neutrophils is to have a clinical suspicion of phagocyte disorder ***(Winkelstein et al., 2000).***

Evaluation for phagocytic cell disorders should be initiated among those patients who have recurrent respiratory tract bacterial infections, such as pneumonia, sinusitis and suppurative otitis media; skin infections, as cellulitis or abscesses; lymphadenitis or infections presenting at unusual sites (renal, hepatic, brain abscesses) or caused by unusual pathogens (ie, Aspergillus pneumonia, disseminated candidiasis, Serratia, marcescens, etc) ***(Wolach et al., 2000)***.

The primary disorders of the phagocytic function include chronic granulomatous disease (CGD), hyperimmunoglobulin E syndrome, (HIES), leukocyte adhesion deficiencies (LAD), Chediak- Higashi syndrome (CHS), myeloperoxidase deficiency (MPO) and white cell G6PD deficiency (enzyme level less than 1%) ***(Wolach et al., 2000)***.

On the other hand, the number of patients with recurrent bacterial infections and suspected impairment of neutrophil function largely exceeds the incidence of well-characterized congenital defects of neutrophils ***(Brenneis et al., 1993)***.

Aim of the Work

The aim of this study was to evaluate the neutrophil function in a group of Egyptian children with proved primary immunodeficiency diseases and another with unexplained recurrent, severe, or unusual bacterial and /or fungal infections. The relationship between neutrophil dysfunction and type and severity of infections was as well evaluated.

Chapter one

Neutrophil Development and Function

Neutrophils are a critical cellular component of the innate immune response to invading microorganisms. As such, primary alterations in their number or function can result in propensity for serious, often life threatening infections. Children with primary neutrophil function defects present predominantly with low-grade chronic bacterial or fungal infections, these infections tend to be persistent and difficult to resolve with standard treatment. Overt bacterial sepsis is an unusual finding at presentation ***(Wolach et al., 2000).***

I. Neutrophil development:

Developmental hematopoiesis occurs in three anatomic stages: ***mesoblastic, hepatic, and myeloid***. ***Mesoblastic hematopoiesis*** occurs in extra embryonic structures, principally in the yolk sac, and begins between the 10^{th} and 14^{th} days of gestation in which neutrophils are first observed in the human fetus about 5 weeks postconception as small clusters of cells around the aorta. ***Hepatic hematopoiesis*** takes place by 6–8^{th} week of gestation in which the liver replaces the yolk sac as the primary site of blood cell production. While ***myeloid hematopoiesis*** takes place by 10–12^{th} week, in which the fetal bone marrow space begins to develop around the 8^{th} week post