

# **TUMOR NECROSIS FACTOR IN ACUTE RHEUMATIC FEVER**

**Thesis  
submitted for partial fulfillment of  
Master Degree in Pediatrics**

**By  
Amal Abd El-Maksoud Kamal  
(M.B., B.Ch)**

**Under supervision of**

**Prof. Dr. SAWSAN AMIN EL-SOKKARY**  
Professor of Pediatrics  
Ain Shams University

**Dr. HISHAM ABDEL SAMIE AWAD**  
Lecturer of Pediatrics  
Ain Shams University

**Dr. AZZA SADEK EL-DANASOURY**  
Lecturer of Clinical Pathology  
Ain Shams University

**Faculty of Medicine  
Ain Shams University  
1994**

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

اقْرَأْ بِاسْمِ رَبِّكَ الَّذِي خَلَقَ

خَلَقَ الْإِنْسَانَ مِنْ عَلَقٍ

اقْرَأْ وَرَبُّكَ الْأَكْرَمُ الَّذِي عَلَّمَ بِالْقَلَمِ

عَلَّمَ الْإِنْسَانَ مَا لَمْ يَعْلَمْ

المستق. ١٠-٥



**TO  
MY LOVELY SON  
KAMAL EL-DIN**

## ACKNOWLEDGEMENT

I would like to express my sincere gratitude and deepest thanks to Prof. Dr. **SAWSAN AMIN EL-SOKKARY**, Professor of Pediatrics, Ain Shams University, for her valuable advice, continuous guidance and support throughout this work.

My special deepest thanks to Dr. **HISHAM ABDEL SAMIE AWAD**, Lecturer of Pediatrics, Ain Shams University, for his kind help, careful guidance and supervision during every step of this work.

I wish to express my deepest thanks to Dr. **AZZA SADEK EL-DANASOURY**, Lecturer of Clinical Pathology, Ain Shams University, for her valuable assistance in this work.

I would like to thank my **Parents** and my **Husband** for their continuous encouragement and cooperation.

## LIST OF ABBREVIATIONS

- Anti-nDNA : Anti-native deoxyribonuclear antibody.
- ATPase : Adenosine triphosphatase.
- BCG : Bacillus Calmette Guerin.
- CRP : C-reactive protein.
- DNA : Deoxyribonucleic acid.
- ELISA : Enzyme linked immunosorbent assay.
- ESR : Erythrocyte sedimentation rate.
- IFN-gamma : Interferon-gamma.
- Ig : Immunoglobulin.
- IL-1 : Interleukin-1.
- KD : Kilo dalton.
- LPS : Lipopolysaccharide.
- rhTNF-alpha : Recombinant human TNF-alpha.
- rTNF-alpha : Recombinant TNF-alpha.
- TNF-alpha : Tumor necrosis factor alpha.

## LIST OF FIGURES

- Figure (I): Mechanism of action of TNF-alpha .....(47)
- Figure (1): Mean ESR level before and after  
treatment .....(84)
- Figure (2): CRP before and after treatment .....(86)
- Figure (3): Mean TNF level before and after  
treatment .....(87)
- Figure (4): Correlation between TNF and ESR before  
treatment .....(88)
- Figure (5): Correlation between TNF and ESR after  
treatment .....(89)

## LIST OF TABLES

- Table (1): Fundamental of diagnosis of rheumatic fever .....(22)
- Table (2): Guide for bed rest and ambulance .....(35)
- Table (3): Recommended anti-inflammatory agents for acute rheumatic fever .....(35)
- Table (4): Mediators stimulated by cachectin/TNF .....(56)
- Table (5): The clinical data of 20 patients with differenttypes of rheumatic fever .....(76)
- Table (6): The sex difference in rheumatic arthritis .(78)
- Table (7): The sex difference in rheumatic carditis ..(79)
- Table (8): The sex difference in rheumatic chorea ....(80)
- Table (9): The sex distribution among each studied group of patients .....(81)
- Table (10): The values and the mean and SD of ASOT of the study group .....(82)
- Table (11): The mean and SD of ESR before and after treatment .....(83)
- Table (12): The mean and SD of TNF before and after treatment .....(85)
- Table (13): The age, sex and TNF values of the control group .....(90)
- Table (14): The mean and SD of the values of TNF in 20 patients with rheumatic fever before and after one month of treatment versus to the control group .....(91)



## TABLE OF CONTENTS

-INTRODUCTION AND AIM OF THE WORK .....	(1)
-REVIEW OF LITERATURE .....	(3)
* Rheumatic fever .....	(3)
* Tumor necrosis factor alpha .....	(43)
* Tumor necrosis factor alpha in rheumatic fever ..	(60)
-SUBJECTS AND METHODS .....	(66)
-RESULTS .....	(76)
-DISCUSSION .....	(92)
-SUMMARY AND CONCLUSION .....	(103)
-RECOMMENDATIONS .....	(106)
-REFERENCES .....	(107)
-ARABIC SUMMARY.	

# INTRODUCTION AND AIM OF THE WORK

## INTRODUCTION

Rheumatic fever is frequently classified as a connective tissue disease because its anatomical hallmark is damage to collagen fibrils and to the ground substance of connective tissues (especially in the heart). Its difference from other rheumatic diseases is that it is specifically a delayed non suppurative sequelae of pharyngeal infection with group A streptococci (Stallerman, 1992).

Human tumor necrosis factor-alpha (TNF-alpha) also named cachectin is a 157 a.a unglycosylated polypeptide cytokine mainly produced by activated macrophage (monocytes). Among the biological activities of TNF-alpha we can mention the metabolic activities, antitumoral growth regulatory activities, immunomodulatory and proinflammatory activities. In fact, TNF activates macrophages/neutrophils and eosinophils as well as endothelial cells. It regulates the production of antibodies by B cells and stimulates cytotoxic cells. It induces the production of several other inflammatory mediators such as IL-1, IL-6, colony stimulating factor and collagenase. TNF-alpha often in combination with other cytokines has also been involved in several autoimmune diseases (Miller, 1989).

because of importance of soluble mediators of the immune response in various rheumatic diseases we speculated whether abnormalities in production of these mediators would be found in sera from patients with rheumatic fever.

**AIM OF THE WORK:**

To study the level of TNF in different types of rheumatic patients whether rheumatic heart disease, rheumatic chorea or rheumatic arthritis in correlation to disease activity before and after treatment.

# REVIEW OF LITERATURE

## **RHEUMATIC FEVER**

### **Introduction:**

Rheumatic fever is frequently classified as a connective tissue disease because its anatomical hallmark is damage to collagen fibrils and to the ground substance of connective tissue (especially in the heart). Of major clinical importance is the presence of potentially lethal myocarditis during the acute attack or, more commonly, the fibrosis of the heart valves, which leads to the crippling hemodynamics of chronic rheumatic heart disease. Its difference from other rheumatic diseases is that it is specifically a delayed non suppurative sequel of pharyngeal infection with group A streptococci (Stallerman, 1992).

### **The Infecting organism:**

The group A  $\beta$ -hemolytic streptococcus is a unicellular bacterium composed of a core of cytoplasm enclosed in a thin cytoplasmic membrane which in turn is surrounded by a rigid cell wall of three layers: an inner mucopeptide layer, a middle layer of group specific carbohydrate, and an outer protein layer, the chief component of which is M protein the major antigen implicated in pathogenesis.

External to the cell wall is a large capsule of hyaluronate which imports a mucoid appearance to the bacterial colonies on culture plates, this property is also associated with virulence.

Fimbriae, made up of M protein and lipoteichoic acid, project from the outer surface of the bacterial cell giving it a "hairy" appearance on E/M, these fimbriae unable it to adhere to host epithelial cells (Haffejee, 1992).

The ability of the group A streptococcus to cause infection is attributed primarily to the surface located M protein, an alpha-helical coiled-coil fibrillar molecule that confers to the organism the ability to resist phagocytic attack (Vincent et al., 1989).

The attachment of the bacteria to the pharyngeal wall occurs between an M protein-lipoteichoic acid complex on the streptococcal surface and fibronectin on the pharyngeal cell membrane.

Adherence may be considered a necessary pre-requisite to virulence. Antigenic difference in M protein allow for immunological subclassification of group.