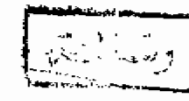
WISKOTT - ALDRICH SYNDROME

ESSAY
Submitted for Partial Fulfillment
of Master Degree in
Dermatology and Venereology

By
Khaled Hishmat El-Feky
M.B., B.Ch.
Ain Shams University



Under Supervision of
Prof.Dr. Hoda Rifaat El-Mazny
Professor of Dermatology and Venereology
Faculty of Medicine
Ain Shams University

54776

616.5075
Kh . H

Dr. May Hussein El-Samahy
Lecturer in Dermatology and Venereology
Faculty of Medicine
Ain Shams University

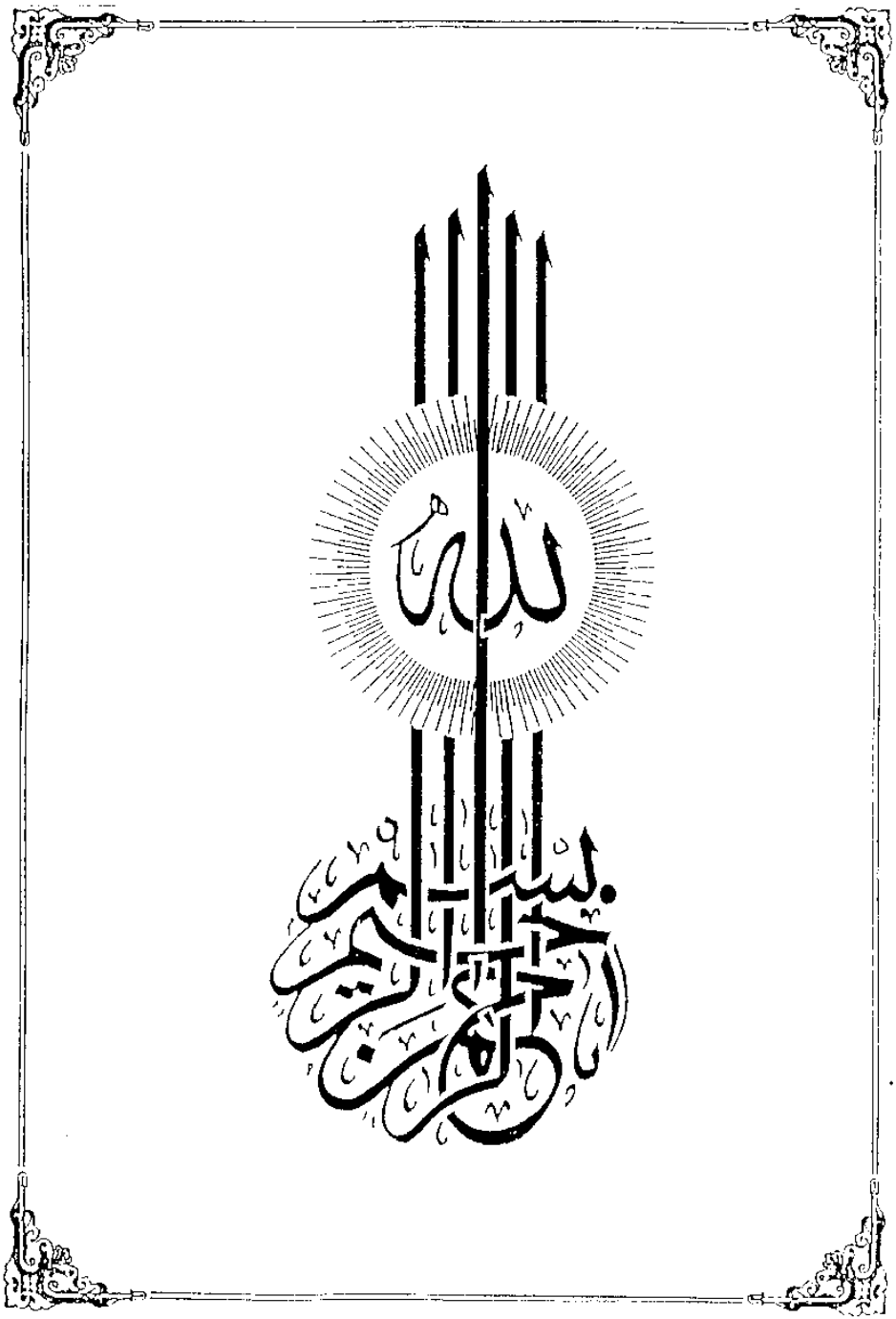
FACULTY OF MEDICINE
AIN SHAMS UNIVERSITY
1994

بسم الله الرحمن الرحيم

﴿وقل رب زدني علماً﴾

"صدق الله العظيم"

(سورة طه آيه رقم (١٤)



Central Library - Ain Shams University

To everyone taught me a letter,,

To my parents ...

To my wife ...

Acknowledgment

First and foremost, thanks to God.

I would like to express my sincerest gratitude, all apperciation, utmost respect to **Prof. Dr. Hoda Rifaat El-Mazny,** *Professor of Dermatology and Venereology, Ain Shams University, for her kind help, guidance, and encouragement throughout the course of this work.*

I do feel greatly indebted to **Dr. May Hussein El-Samahy,** *Lecturer in Dermatology and Venereology, Ain Shams University, for her kind guidance, for her patience and her continuos help in the work.*

Last but not least, I wish to extend my thanks to all the staff members of the Dermatology and Venereology Department; Ain Shams University, for their encouragement and help in achievement of this work.

CONTENTS

	Page
Introduction and Aim of the Work	1
Review of Literature	4
• Historical review	4
• Etiology and Pathogenesis	8
• Clinical Aspects	22
• Laboratory Aspects	31
• Genetic Counseling	37
• Therapeutic Approaches	46
Summary and Conclusion	54
References	58
Arabic summary	---

INTRODUCTION AND AIM OF THE WORK

INTRODUCTION AND AIM OF THE WORK

The Wiskott-Aldrich syndrome (WAS) is an inherited X-linked recessive immunodeficiency disorder characterized by recurrent infections, eczema, and thrombocytopenia[1].

The first description of the WAS as a distinct clinico-pathological entity was provided in 1937 by a German physician named Wiskott[2]. Aldrich enhanced the understanding of this disorder in 1954 with an elegant description of a large pedigree with a sex-linked recessive condition characterized by draining ears, eczematoid dermatitis and bloody diarrhea[3].

It has been estimated from population-based incidence rates that a minimum of six patients with WAS are born each year in the United States[4]. Therefore, as for most primary immunodeficiencies, the incidence of WAS is rare. However, these figures under estimate the true incidence rate because of the common failure to diagnose WAS in sporadic cases and in patients with the milder, variant forms of the syndrome[5].

Although WAS typically has a triad of signs, two milder diseases have been cited as WAS variants: an X-linked form of

thrombocytopenia[6] and a WAS like syndrome associated with renal disease[7].

WAS is associated with a 100 fold increased risk of malignancy[4]. Approximately two-thirds of the malignancies are non-Hodgkin lymphomas, often originating in extranodal sites[8].

The underlying biochemical defect in WAS is believed to be expressed primarily by cells derived from the bone marrow, all other WAS manifestations, including the eczematous skin lesions, arise as a result of this defect[5]. The etiology of WAS is unknown, although its genetic locus has been mapped to the pericentromeric region of the short arm of the X-chromosome[9].

Patients with WAS have impaired T- and B-lymphocyte function manifested as absent delayed hypersensitivity, reduced circulating T-cells with diminished mitogen and antigen stimulated responsiveness, reduced numbers of T-helper cells with abnormal T-helper/T-suppressor cell ratios, low serum levels of IgM, and impaired antibody responses to polysaccharide antigens[10].

Unless the condition is treated by bone marrow transplantation, the prognosis of WAS is grave and premature death caused by sepsis, heamorrhage, or lymphoreticular malignancy is common[5].

The aim of the work is to review the clinical and laboratory features of this syndrome and to summarize the new molecular and biochemical approaches that can be used in diagnosis, genetic counseling and treatment.

REVIEW OF LITERATURE

HISTORICAL REVIEW

HISTORICAL REVIEW

An inherited type of thrombocytopenia associated with eczema and reccurent infections usually having a fatal outcome has been described by Wiskott[2] in a German family whose three male infants died from the symptom complex in 1937. Aldrich et al.[3], in U.S.A., reviewed a family history over six generations, in which 16 male infants died from complaints similar to that of their patient in 1954. They suggested that the disease was inherited as a recessive sex-linked disorder.

Three years later, about 50 cases, mostly from the U.S.A. and some from the Continent, have been described, including six cases in a Negro family[11]. In some of these there was no family history. In an English family two affected brothers have been described in 1960 by Gordon[12]. The elder had a splenectomy at the age of four years. In the following year he began to have recurrent infections, including meningitis, which he survived. Some months later he died from coma of unknown cause.

Extensive research work continued to place this disease within the spectrum of known disorders and to clarify the nature of the defect leading to such clinical picture. Cassimos et al.[13], in studying the immunological causes of their cases of

WAS, found low titres of isoagglutinins; Eitzman and Smith[14] noted a relative deficiency of IgM in such patients. Gelzer and Gasser[15] observed morphological abnormalities of platelets, such as small size, absence of a central halo, and poor granulation. They also noted that serum levels of some amino acids were low. Cooper et al.[16] have demonstrated deficient delayed hypersensitivity responses.

Immunological investigations were carried out in eleven patients with the WAS in 1968 by Blease et al.[17]. They concluded that WAS patients have a broad immunological defect involving both humoral and cellular immune responses. Such a broad defect associated with the presence of functional lymphocytes and adequate immunoglobulin levels suggests that the defect may be in the recognition or processing of antigens, in the proper transfer of the immune message to the effector cells, or in the reading of the message by the effector cells. Such defects would be in the afferent limb of immunity.

As a result of extensive research work, it was postulated that, in addition of the three primary problems which define WAS clinically, many patients have a variety of secondary complications, the most significant being malignancy[18]. This syndrome was the association between immunodeficiency and

malignancy that first interested the pathologists and immunologists who proposed the creation of the Immunodeficiency-Cancer Registry (ICR) in 1971[19].

In 1972, the ICR began its formal collection of pathologic and clinical data on all patients with immunodeficiency who developed malignancy. In 1975 as an outgrowth of the ICR work, a separately funded study began to collect WAS case information and detailed family histories to evaluate the occurance of malignancy in WAS families[4].

In the past, the therapeutic approach to WAS included mostly palliative measures that dealt with bleeding and infections. Since then, a major advance, bone marrow transplantation, has significantly increased survival and has provided a better quality of life for boys with this disorder[5]. It was first attempted in the late 1960s[20], but successful correction of the defects associated with WAS by allogeneic bone marrow transplantation from an HLA-identical sibling was reported by Parkman et al.[21] in 1978.

Despite extensive research efforts, the genetic locus, the underlying biochemical defect and the molecular basis of WAS remain unknown[5], also selective inactivation of the X-