IMMUNOLOGICAL STUDIES IN PATIENTS WITH IDIOPATHIC DILATED CARDIOMYOPATHY

Thesis

Submitted in Parital Fulfilment

for the Requirement of (M.D) in Clinical Pathology

By

MAHA ALI EZZ EL DIN
M.B.B.Ch
Master degree of clinical pathology

Supervised by

Prof. Dr. AIDA ABD EL AZIM ABD EL SALAM
Professor of Clinical Pathology

Prof. Dr. LAILA ABOU EL MAGD
Professor of Clinical Pathology

Prof. Dr. AMANI IBRAHIM SALEH
Assistant Professor of Clinical Pathology

Prof. Dr. OMAR AWAD
Professor of Cardiology

Faculty of Medicine

Ain Shams University

1991

ACKNOWLDGEMENTS

I would like to express my sincere and deep gratitude to Professor Doctor Aida Abd El Azim, Professor of clinical pathology, Ain Shams University, for her supervision and kind suggestion.

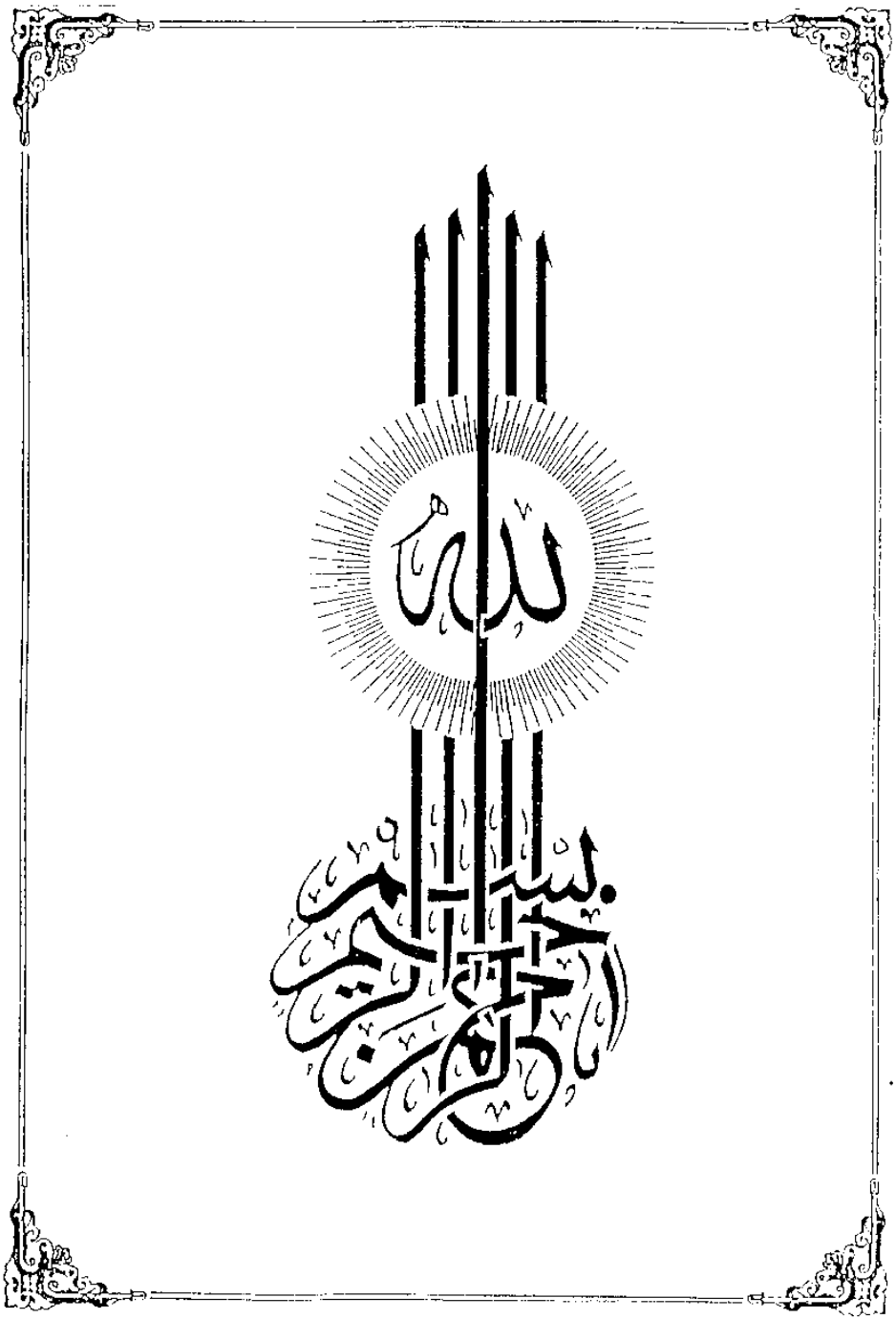
I am also deeply grateful to Professor Doctor Laila Abou El Magd, Professor of clinical pathology, Ain Shams University, for her support and continuous help.

I would like to express my deepest gratitude and appreciation to Professor Doctor Amani Ibrahim Saleh, Assistant Professor of clinical pathology, Ain Shams University, for her continuous help and valuable advice and guidance throughout the whole work.

I owe special thanks to Professor Doctor Omar Awad, Professor of cardiology, Ain Shams University for his valuable suggestions concerning this work.

I also wish to thank Doctor Aisha Yassen, lecturer in clinical pathology, Ain Shams University for her help and support.

I also wish to thank Doctor Tarek Zaki, lecturer of cardiology, Ain Shams University, for his help in cases selection.



IMMUNOLOGICAL STUDIES IN PATIENTS WITH IDIOPATHIC DILATED CARDIOMYOPATHY

CONTENTS

I- INTRODUCTION

AND AIM OF THE WORK.

INTRODUCTION AND AIM OF THE WORK

INTRODUCTION:

Idiopathic dilated cardiomyopathy (IDCM) is relatively common in Africa and account for high morbidity and mortality (Vaughan, 1977).

Goodwin (1982) and Matsumoi and Kawai (1982) suggested that the immune system may be involved in the pathogenesis of IDCM. Disorders of absolute or relative number or function of various mononuclear cell subsets have been described for several diseases with autoimmune features. Abnormal humoral, cellular and immunoregulatory response have been described in several studies concerned with IDCM (Anderson et.al., 1982 and Gerli et.al., 1986). These abnormal responses include deficiency in suppressor T Lymphocytes and natural killer cell activity (Anderson et.al., 1985)

Humoral mechanisms have also been investigated and anti-heart antibodies of uncertain significance have been observed in some cases (Bolte, 1978 and Yamakawa et.al., 1987).

A high incidence of lymphoma in patients who recieve immunosuppressants after heart transplantation for IDCM may be related to immune aberration associated with IDCM (Anderson et.al.,1978).

The role of viral infection of the heart progressing to IDCM has recieced considerable attention (Cassling et.al., (1985), and a link with immunoligical abnormalities has been proposed (Goodwin, 1982). Animal studies suggest that alterations in the immune status at the time of viral infection may influence the type and extent of damage to the myocardium in short and long term (Kawai et.al, 1978). Alternatively once a virus has initiated damage, abnormal immnological mechanisms may then prepetuate the damage of the myocardium and lead to IDCM (Wong et.al, 1977).

AIM OF THE WORK:

In this study a trial is made to find the immunological changes which are present in IDCM in a group of Egyptian patients and wether they are considered as primary aetiological causes or a consequence of the disease.

II- REVIEW OF LITRATURE

IMMUNOLOGICAL REACTIONS IN HEART DISEASES

Immunological mechanisms play a part in diseases of the heart as they do in every other organ of the body. The understanding of the pathologic role of these reactions has changed since the first suggestion that a number of chronic inflammatory disorders are in fact autonomus and self destructive autoimmune diseases (Lessof, 1978).

Autoantibodies, which react with the body's own tissues are found in some, but by no means all of the chronic diseases. They may be specific for such tissue as thyroid or heart, or can react less specifically, with a wide variety of nuclei, mitochondria, or cell products (Roitt, 1989). Even when an autoimmune response is evident, and autoantibodies are found in associaton, it sometimes represents the indirect result of infection and mopping up reaction to tissue breakdown. Such a reaction includes local lymphocytic infiltration besides a wide variety of cells, some of which also have a regulatory effect on antibody production. If this response is inadequate as it seems to be in systemic lupus, a defeciency of suppressor T lymphocytes may result. This appears to lead to further rise in the production of antibodies, including those antibodies which are capable of reacting with the body own tissues (Bresnihan and Jasin,1977).

Of the four classical types of hypersensitivity reactions there is little evidence of immediate allergy and anaphylaxis in the heart (type I) but ther other types of responses may be present in any combination. Cytotoxic can either destroy cells (type II) or stimulate an attack by killer lymphocytes. Immune complexes of antigen and antibody trapped within small blood vessels, can trigger the complement system of enzymes and cause both an imflammatory reaction and an activation of the clotting sequence (type III). There may be extensive tissue damage associated with lymphocyte infiltration (Type IV) (Lessof, 1978).

ANTI HEART ANTIBODIES IN HEART DISEASES:

The presence of antiheart antibodies cannot explain the presence of cardiac damage, since they have been reported in the serum of wide range of diseases. They have been described in the postpericardiotomy syndrome (De Scheerder et.al., 1985 and Zabriski. et.al., 1981) in infectious endocarditis (Das & Cassidy, 1977), in rheumatic fever and primary myocardial disease (Bolte and Grothe, 1977, Sachs. et.al., 1986), and in coronary artery disease (Bauer. et.al., 1972 and De Scheerder. et.al., 1984). Heart antibodies have also been detected in patients with congestive and hypertrophic cardiomyopathies by some investigators (Trueman. et.al, 1981), and in glomerulonephritis and rheumatoid arthritis (Hess. et.al, 1964). These findings suggest that these antibodies lack specifity or that their production represents a secondary reaction to damaged heart muscle cell. In support of the first of these explanations, the well known affinity of syphilitic serum for cardiolipin provides a reminder that non specific reactions may sometimes appear to be directed predominantly against heart muscle. In support of the second explanation, it has been noted that there is an increase in detectable antiheart antibodies for two or three weeks after a myocardial infarct (Kuch, 1973). In addition, it has been shown in dogs by Pinckard and his colleagues (1971) that cardiac infarcts produced by coronary ligation, or by the intra-arterial injection of microspheres, are nearly always followed by the release of antiheart antibodies, appearing about ten days after the infarction and disappearing within four to six weeks.

HEART DISEASES WITH IMMUNOLOGICAL FEATURES:

In proposing the concept of rheumatic fever as an autoimmune diseases, Kaplan and Meyeserian (1962) suggested that an infection with B-haemolytic streptococci can stimulate the production of antibodies which cross react with heart muscle cells. Antibodies to streptococcal cells have not been shown to damage the heart muscle but nevertheless have an affinity for the sarcolemmal and subsarcolemmal sarcoplasm of heart muscle fibers. This affinity is lost when the serum is absorbed with streptococcl cell membranes M-protein, which is a factor associated with virulence in group (A) B-haemolytic streptococci appeared to be involved in this cross reaction, and there is also evidence of lymphocyte

mediated delayed hypersensitivity to streptococcal products (Read. et.al., 1974; Sapru. et.al., 1977 and Roitt, 1989). Anderson et.al.(1981), recorded that a chronic immunoregulatory defect does not appear necessary for the development of rheumatic heart diseases.

The concept of an autoimmune reaction provoked by an infection is echoed by the findings in Chagas disease, in which diagnostically useful endocardial vascular interstitial factor (EVI) antibody is detectable in most patients with chronic cardiomyopathy. This antibody react with intersitia tissue, endocardium, and vascular endotheilum, but is absorbed by antigens from the causative agent, Trypanosoma Cruzi. Cytotoxic T cells have a destructive effect against Trypanosoma Cruzi, in which autoimmune destruction of parasitized heart cells and fibroblasts has been demonstrated (Cossio et.al, 1974)

As far as the heart is concerned, patients with chronic heart block have an increaed prevalence of vitiligo, hypothyrodism, and pernicious anaemia (Fairfax and Letham, 1975), diseases which are all associated with striking evidence of autoimmunity. Many of these patients have an idiopathic fibrotic process in the conducting process in the conducting tissue, with scanty inflammatory infiltration (Davies, 1971), but the underlying myocardium, which has the same blood supply, is spared. Fairfax (1977) has reported that a small group of patients with longstanding heart block possess a serum antibody which reacts with Prukinjie tissue but not cardiac muscle, this emphasises the antigenic differences between conducting tissue and myocardium.

The postpericardiotomy syndrome is a frequent complication after cardiac surgery. It is characterized by the persistance or occurence of fever, leucocytosis and signs of pericardial and often pleural reaction, frequently with effusion and pneumonitis after the first postoperative week (Maish et.al., 1979). Dresseler (1956 and 1959) had described a similar illness, the post-acute myocardial infarction. Since other forms of cardiac injury give rise to a similar complication, this syndrome is now generally referred to as post cardiac injury syndrome. Although these syndromes are strikingly similar and have been well defined clinically their pathogenesis remain unclear. The clinical observation that these syndromes appear seven or more days after the acute injury and are sensitive to

corticosteroid therapy suggests that immunologic factors are involved in their pathogenesis (De Scheerder. et.al., 1985). The finding of antiheart antibodies (Maish. et.al., 1979) and circulating immune complexes (De Scheerder. et.al., 1984) in sera of most of these patients supports this view. Lessof (1978) reported that in post-cardiac injury syndrome, the growth or reactivation of a virus may lead to tissue damage and this can, as in other infectious diseases, lead to autoantibody formation and immune complex deposition.

Mathews et.al. (1974) suggested that immune complexes are circulating in the blood of arteriosclerotic patients, and that these complexes play a role in the pathogenesis of vascular disease, and the highest incidence of such complexes was found in myocardial infarction (Fuster et.al, 1981).

The role of autoantibodies against cardiac tissue in acute myopericarditis is poorly understood. Kurki et.al. (1989) found that autoantibody (Anti-desmin antibody) was high in the acute phase of acute infectious myopericarditis and declines during recovery.

Klema et.al. (1988) and Mattila et.al (1989) found an increase in anticardiolipin antibodies in myocardial infarction and in angina pectoris. Manoussakies et.al. (1987) detected anticardiolipin antibodies in rheumatic diseases.

Cardiomyopathies are diseases in which autoimmune reaction may play a role in pathogenesis. In idiopathic dilated cardiomyopathy (IDCM), aberrant immune mechanism were found to play a role (Robinson and O'Connell, 1983).

THE CARDDIOMYOPATHIES

DEFINITION:

"Cardiomyopathies are heart muscle diseases of unknown causes" (WHO, ISFC, 1980)

HISTORICAL ASPECTS OF CARDIOMYOPATHY:

Three decades ago, the frontiers of cardiomopathy were illdefined and nebulous, as there is no working definition or classification had been suggested, and delineation was imprecise. The cardiomyopathies were often confused with myocarditis, a term used widely in a variety of pathological and clinical contexts without clarity of expression. Myocarditis was sometimes equated with cardiomyopathy and sometimes with a specific inflammatory disorder (Goodwin, 1979).

In 1957, Brigden published his lecture on "uncommon myocardial diseases, the non coronary cardiomyopathies". Brigden pointed out the diversity of the disorder and the difficulty of classification. He was among the firsts to use the term " cardiomyopathy ".

In 1964, Goodwin. et.al. defined cardiomyopathy as follows " cardiomyopathy: an acute, subacute or chronic disorder of heart muscle of unknown or obscure aetiology, often with associated endocardial or sometimes with pericardial involvement but not atherosclerotic in origin ". The authors suggested that cardiomyopathies might present clinically in one of three ways; congestive, constrictive or obstructive.

In 1972, Goodwin and Oakley simplified the definition of cardiomyopathy to "a disorder of cardiac muscle of unknown cause". This concept has not always been readily accepted, but it has received approval from the World Health Organisation and International Society and Federation of Cardiology

(WHO/ISFC, 1980). The concept of classification was based upon the disorders of structure and funtion of heart muscle.

It has been recognised that the 'obstructive cardiomyopathy, type is mainly for massive ventricular hypertrophy and imapaired diastolic function, so the definition was revised to "hypertrophic obstructive cardiomyopathy" (Cohen. 1964). At this time it was generally agreed that obstruction to outflow of the left ventricle was an important feature of the condition, though it had been recognised that in some patients no obstruction existed. Swan. et.al. (1971) noted that as the disease became more severe the signs of obstruction tended to disappear.

In addition to the hypertrophic, congestive and constrictive types a new group was introduced, that of obliterative cardiomypathy, to indicate the effects of endomyocardial fibrosis in obliterating the cavity of the ventricle (Goodwin, 1970 and 1974).

CLASSIFICATION OF CARDIOMYOPATHY:

According to the report of WHO/ISFC (1980) cardiomyopathy has been classified into:

- Dilated cardiomyopathy.
- Hypertrophic cardiomyopathy.
- Restrictive cardiomyopathy.

Dilated cardiomyopathy:

The condition is recognised by dilatation of the left or right ventricle, or both ventricles. Dilatation often becomes severe and is invariably accompanied by hypertrophy. Systolic ventricular function is impaired. Congestice heart failure may or may not supervene. Presentation with disturbances of ventricular or atrial rhythm is common , and death may occur at any stage.

Hypertrophic cardiomyopathy:

This condition is characterized by disproportionate hypertrophy of the left ventricle and occasionally also of the right ventricle, which typically involves the septum more than the free wall but occasionally is concentric. Typically, the left ventricle volume is normal or reduced. Systolic gradients are common.

Inheritance is usually by an autosomal dominant gene with incomplete penetrance. Characteristic morphological changes are usually most severe in the septum.

Restrictive cardiomyopathy:

This may exist either with or without obliteration. Restrictive cardiomyopathy includes endomyocardial fibrosis and Loffler's cardiomyopathy. It is proposed that this condition should be referred to as an eosinophilic endomyocardial disease.

Endomyocardial scarring usually affects either one or both ventricles, and restricts filling . Involvement of the atrioventricular valves is common, but the outflow tracts are spared. Cavity obliteration is charachteristic of advanced cases.

" Unclassified cardiomyopathy " covers a few cases which do not fit readily into any group. This includes some with minor abnormalities in which progression to overt cardiomyopathy may not occur. This has been referred to as latent cardiomyopathy.