HIDDEN RHEUMATOID FACTOR IN SERONEGATIVE RHEUMATOID ARTHRITIS, AND SERONEGATIVE ARTHROPATHIES

THESIS
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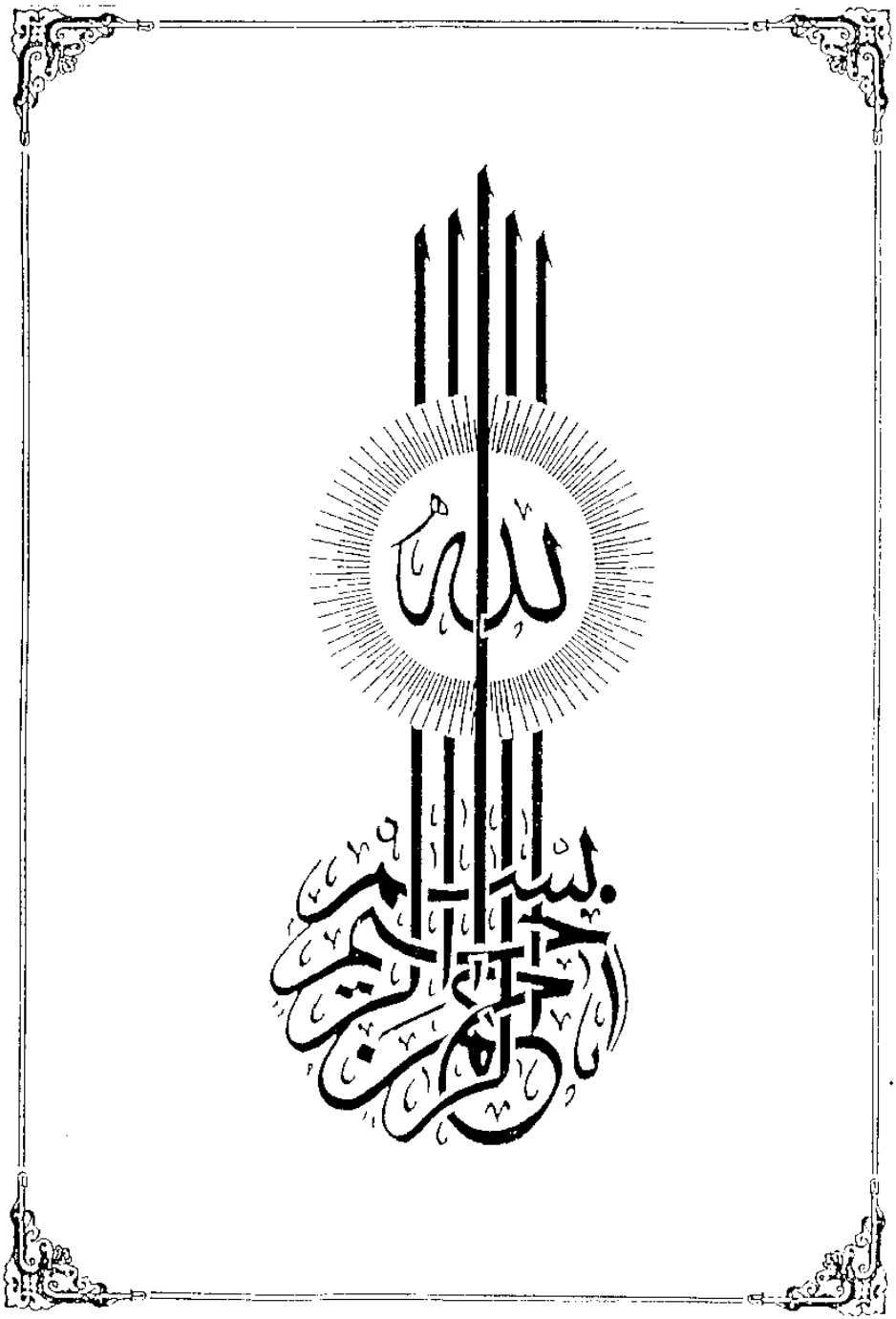

CONTENTS

LIST OF ABBREVIATIONS

ACL	= Anti-cardiolipin.
ACR	= American Collage of rheumatology.
AEA	= Anti-endothelial cell antibodies.
ANA	= Anti-nuclear antibodies.
ANCA	= Anti-neutrophil cytoplasmic antibodies.
anti-RANA	= anti-RA associated nuclear antigen.
anti-RNP	= Anti-ribonucleoprotein.
APF	= Anti-perinuclear factor.
ARA	= American Rheumatism Association.
AS	= Ankylosing spondylitis.
ASOT	= antistreptolysin-O titer.
CIC	= Circulating immune complexes.
CMV	= Cytomegalovirus.
CRP	= C-reative protein.
EBV	= Epstein Barr Virus.
ELISA	= Enzyme Linked immunosorbent assay.
ESR	= Erythrocyte sedimentation rate.
HLA	= Human leukocyte antigen.
HRF	= Hidden rheumatoid factor.
HSP	= Heat shock protein.
IC	= Immune complex.
IFN-δ	= Gamma-interferon.
IL-	= Interleukin--
JCA	= Juvenile chronic arthritis.
JRA	= Juvenile rheumatoid arthritis.
LFT	= Latex fixation test.
MCP	= Metacarpophalangeal.
MTP	= Metatarsophalangeal.

LIST OF ABBREVIATIONS (Continued)

n-DNA	= Native-deoxyribonuclic Acid.
PFC	= Plaque-forming cell.
PG	= Proteoglycan.
PGE_2	= Prostaglandin E_2.
PMN	= Polymorphonuclear.
PIP	= Proximal interphalangeal.
RA	= Rheumatoid arthritis.
RCRI	= Rheumatoid factor cross reactive idiotype.
RF	= rheumatoid factor.
RIA	= Radioimmunoassay.
RW	= Rose-Waaler test.
S.JRA	= Systemic - JRA
SCAT	= Sensitized sheep cell agglutination test.
SIL-2r	= Soluble interleukin-2 receptors.
SLE	= Systemic lupus erythematosis.
SRBC	= Sheep red blood cells.
TNF-	= Tumor necrosis factor-

Introduction

INTRODUCTION

Rheumatoid arthritis (RA) is the commonest chronic inflammatory disease of the joints. There is overwhelming evidence that the immune system is involved in RA.

Rheumatoid factors may play an important role in sustaining inflammation in RA. They can form immune complexes which are taken up by the polymorphonuclear cells (PMN) and are also thought to activate complement, both mechanisms for generating inflammation, and it is well known that RF positivity is associated with more severe and active disease *(Walker et al., 1986)*.

Hidden 19S IgM RF (HRF), i.e., 19S IgM RF detected in the IgM containing fraction of serum after separation by acid gel filtration, were initially described by Allen and Kunkel (1966) in adults with severe RA who were seronegative for 19S IgM RF by the latex fixation test (LFT). Moore et al., (1978) first showed the presence of hidden 19S IgM RF in children with JRA. They found HRF in 59-68% of children with seronegative JRA. Elevated titers of HRF in seronegative patients have been shown to be strongly associated with JRA patients *(Moore et al., 1978)* and to correlate with disease activity *(Moore et al., 1982)*.

Aim of the work

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The aim of this study is to evaluate the role of HRF among Egyptian rheumatoid arthritis patients, both adults, juvenile and seronegative arthropathies, and its possible use in helping the diagnosis and judging the prognosis of the disease activity.

Review of Literature

RHEUMATOID ARTHRITIS

Introduction:

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder of unknown aetiology characterized by joint involvement. Although it usually manifests during the third to fifth decades of life, it can affect all age groups. RA affects approximately 1-2% of adult population worldwide. Its prevalence increases with age, and it affects twice as many women as men. By the age of 55, nearly 5% of women and 2% of men have the disease. Recent data have demonstrated that the long term outlook for patients who have RA is far worse than was previously believed. In addition to the high incidence of disability, it has become clear that RA accelerates mortality as well, particularly in those who have more advanced disease and extra-articular features *(Golbus, 1993)*.

Articular inflammation is sometimes remitting, but, if continued, it usually results in progressive joint destruction and deformity leading ultimately to variable degrees of incapacitation. Extra-articular features such as rheumatoid nodules, arteritis, neuropathy, scleritis, pericarditis, lymphadenopathy and splenomegaly occur with considerable frequency. They were once thought to be complications of RA, but they are now recognized as integral parts of the disease and serve to emphasize its systemic nature *(Lipsky, 1991)*.

Criteria of diagnosis of RA: *(Table I)*

Difficulties arise both for the clinician and the epidemiologist, because so many cases present with either an incomplete form or atypical features. Thus, provisional diagnostic criteria for clinical and populatiuon studies have been required. In 1958, the American Rheumatism Association (ARA) drew up a set of criteria for establishing the diagnosis of RA. These criteria remained unchanged for many years. They have been of great use, but, in light of current knowledge, they have become outdated *(McCarty, 1993a)*. The American Rheumatism Associatioon Criteria are: *(Ropes et al., 1958)*:

1. Morning stiffness.
2. Pain on motion or tenderness in at least one joint.
3. Swelling (Soft tissue thickening or fluid not boney overgrowth alone), in at least one joint.
4. Swelling of at least one other joint (any interval free of joint symptoms between the 2 joint involvements may not be more than 3 months).
5. Symmetric joint swelling with simultaneous involvement of the same joint on both sides of the body. Bilateral involvement of proximal interphalangeal (PIP), metacarpophalangeal (MCP), or metatarsophalangeal (MTP) joints is acceptable without absolute symmetry. Terminal phalangeal joint involvement will not satisfy this criterion.
6. Subcutaneous nodules over bony prominences on extensor surfaces or in juxta-articular regions.

7. Roentgenographic changes typical of RA, which must include at least bony decalcification localized to or most marked adjacent to the involved joints and not just degenerative changes. Degenerative changes do not exclude patients from any group classified as having RA.
8. Positive agglutination test, i.e., demonstration of the rheumatoid factor (RF) by any method.
9. Poor mucin precipitate from synovial fluid, with shred and cloudy solution. An inflammatory synovial effusion with 2,000 or more white cells/mm3, without crystals, can be substituted for this criterion.
10. Characteristic histologic changes in synovium with 3 or more of the following: a) Marked villous hypertrophy, b) Proliferation of superficial synovial cells often with pallisading, c) Marked infiltration of chronic inflammatory cells, namely lymphocytes or plasma cells, d) Deposition of compact fibrin either on the surface or interstitially. e) Foci of necrosis.
11. Characteristic histologic changes in nodules showing granulomatous foci with central zones of cell necrosis, surrounded by a pallisade of proliferated mononuclear cells, peripheral fibrosis and chronic inflammatory cell infiltration.

According to the presence of some or all of the above criteria, 4 types of RA have been identified:

I- Classical RA:

This diagnosis requires 7 of the above 11 criteria. In criteria 1 through 5, the joint signs or symptoms must be continuous for at least 6 weeks.

II- Definite RA:

This diagnosis requires 5 of the above criteria. In criteria 1 through 5, the joint signs or symptoms must be continuous for at least 6 weeks.

III- Probable RA:

This diagnosis requires 3 of the above criteria. In criteria 1 through 5, the joint signs and symptoms must be continuous for at least 6 weeks.

IV- Possible RA:

This diagnosis requires 2 of the following criteria, and the total duration of joint symptoms must be at least 3 months:

1. Morning stiffness.
2. Tenderness or pain in motion with history of persistance of 3 weeks.
3. History of observation of joint swelling.
4. Subcutaneous nodules.
5. Elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).
6. Iritis.