

ANTINUCLEAR ANTIBODY POSITIVITY IN PATIENTS WITH CHRONIC HEPATITIS C: CLINICALLY RELEVANT OR AN EPIPHENOMENON ?

Thesis

Submitted For partial Fulfillment Of Master
Degree In Internal Medicine

By

MAHMOUD MAHMOUD YOUSIF

M . B . B . CH

Under Supervision of

PROF.DR.MERVAT MAMDOUH ABO GABAL

Professor of Internal Medicine and Rheumatology
Faculty of Medicine
Ain Shams University

DR.ZAINAB AHMED ALI-ELDIN

Assistant Professor of Internal Medicine and Gastroenterology
Faculty of Medicine
Ain Shams University

DR.NORAN OSAMA AHMED EL-AZIZI

Lecturer of Internal Medicine and Rheumatology
Faculty of Medicine
Ain Shams University

**Faculty of Medicine
Ain Shams University
2013**

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

وَقُلْ اَعْمَلُوا فَسَيَرَى اللَّهُ
عَمَلَكُمْ وَرَسُولُهُ وَالْمُؤْمِنُونَ

صَدَقَ اللَّهُ الْعَظِيمُ

Acknowledgement

First, thanks are all due to **Allah** for Blessing this work until it has reached its end, as a part of his generous help throughout our life.

I would like to express my deep gratitude and appreciation to **Prof.Dr.Mervat Mamdouh Abo Gabal**, Professor Of internal Medicineand Rheumatology, faculty Of Medicine, Ain Shams University.

I owe special feeling of gratitude to **Dr.Zainab Ahmed Ali-Eldin**, Assistant Professor Of Internal Medicineand Gastroenterology, Faculty Of Medicine, Ain Shams Universityfor her encouragement, supervision, co-operation and help.

I feel greatly indebted to **Dr.Noran Osama Ahmed El-Azizi**, Lecturer of Internal Medicine and Rheumatology, Faculty Of Medicine, Ain Shams Universityfor her valuable criticism, generous efforts and cooperation during all the stages of this work,

Words are not enough to express my deepest thank feeling and gratitude to **Dr.Moshira Halim Sabry**, MD/Clinical and Chemical Pathology, Faculty of Medicine , Ain Shams University for her great help.

Finally I would like to thanks my parents, my wife and my daughter.



Mahmoud Mahmoud Yousif

CONTENTS

Title	Page
List of tables	I,II, III
List of figures	IV
List of abbreviations	V, VI ,VII
Introduction & Aim of the Work	1
Review of literature	
Hepatitis C virus infection	5
Anti nuclear anti body	54
Antinuclear Antibody in Hepatitis C Virus Infection	71
Patients and Methods	94
Results	104
Discussion	126
Summary and conclusion	135
Recommendation	137
References	138
Arabic Summary	203

LIST OF TABLES OF REVIEW

	Title	Page
Table 1	Indirect Immunofluorescence (IIFA) and enzyme-linked immunosorbent (ELISA) advantages and disadvantages	59
Table 2	ANA immunofluorescent patterns	63
Table 3	Significance of positive ANA test in CTD and some non-autoimmune conditions	64

LIST OF TABLES OF RESULTS

	Title	Page
Table 1	Description of clinical presentation in group 1 (75 patients with chronic hepatitis C at base line).	106
Table 2	Comparison between ANA positive and ANA negative patients in group 1 as regard clinical presentation.	107
Table 3	Comparison between studied groups as regard age and sex.	108
Table 4	Comparison between studied subgroups as regard age and sex.	109
Table 5	Comparison between studied groups in frequency of occurrence of ANA.	110
Table 6	Comparison between ANA positive and ANA negative patients within group 1a as regard age, gender, lab parameters and viral load.	112
Table 7	Comparison between ANA positive and ANA negative patients within group 1a as regard liver biopsy findings.	116
Table 8	Correlation between ANA titer with lab parameters and viral load in group 1a.	118

	Title	Page
Table 9	Comparison between ANA positive and ANA negative patients within group 1b as regard age, gender, lab parameters and viral load.	120
Table 10	Description of liver biopsy findings in group 1b before treatment and its relation with ANA positivity after treatment.	122
Table 11	Comparison between ANA positive and ANA negative patients in group 1b as regard response to therapy.	123
Table 12	Correlation between ANA titer with age, lab parameters and viral load in group 1b.	125

LIST OF FIGURES

	Title	Page
Figures of Review :		
Figure1	Schematic representation of EHM categories	22
Figure2	ANA immunofluorescent patterns	62
Figure3	Pathomechanisms involved in the development of malignant lymphoproliferative disorders	87
Figures of Results:		
figure 1	Correlation between ANA and clinical feature of chronic hepatitis C.	108
figure 2	Frequency of occurrence of ANA in different study groups.	111
figure 3	Mean serum ALT in ANA +ve and ANA-ve patients.	114
figure 4	Mean serum AST in ANA +ve and ANA-ve patients.	114
figure 5	Mean serum creatinine in ANA +ve and ANA-ve patients.	115
figure 6	Comparison between ANA positive and ANA negative patients within group 1a as regard liver biopsy.	117
figure 7	Correlation between ANA titre and serum ALT level in patients of group 1a.	119
figure 8	Comparison between ANA positive and ANA negative patients in group 1b as regard response to therapy.	124
figure 9	Correlation between ANA titre and serum ALT level in group 1b.	126

LIST OF ABBREVIATIONS

AASLD	: American Association for the Study of Liver Diseases
ACAs	: Anti centromere antibodies
AIH	: Autoimmune hepatitis
AIHA	: Autoimmune haemolytic anaemia
AITP	: Autoimmune thrombocytopenia
ALT	: Alanine transaminase
ANA	: Antinuclear antibody
Anti-HBc	: Antihepatitis B core
Anti-HBs	: Antihepatitis B surface
Anti-HCV	: Anti hepatitis C virus
AST	: Aspartate transaminase
BOC	: Boceprevir
cANCA	: Antineutrophil cytoplasmic antibodies
CBC	: Complete blood picture
CLD	: Chronic liver disease
CTD	: Connective tissue disease
DAA	: Direct acting antiviral
ds DNA	: Double-stranded Deoxyribonucleic acid.
EASL	: European Association for the Study of the Liver

LIST OF ABBREVIATIONS (CONT.)

EHM	: Extrahepatic manifestation
ELISA	: Enzyme-linked immunosorbent assay
ENA	: Extractable nuclear antigens
ESR	: Erythrocyte sedimentation rate
HCC	: Hepatocellular carcinoma
IASL	: International Association for the Study of the Liver
IIF	: Indirect immunofluorescence
INF	: Interferon
INR	: International Normalized. Ratio
LKMA	: Liver kidney microsomal antibody
MC	: Mixed cryoglobulinemia
NHL	: Non-Hodgkin lymphoma
NOSAs	: Non organ specific auto- antibodies.
pANCA	: Perinuclear Anti-Neutrophil Cytoplasmic Antibodies
PBC	: Primary biliary cirrhosis
PCR	: Polymerase chain reaction.
RF	: Rheumatoid factor
SLE	: Systemic lupus erythematosus

LIST OF ABBREVIATIONS (CONT.)

SMA	: Smooth muscle antibody
SS	: Sjögren's syndrome
SS CL	: Systemic sclerosis
SVR	: Sustained virological response
WHO	: World health organization

INTRODUCTION

The hepatitis C virus (HCV) is a major public health problem and a leading cause of chronic liver disease. An estimated 180 million people are infected worldwide (**Williams, 2006**). Hepatitis C is an infectious disease primarily affecting the liver, chronic infection can lead to scarring of the liver and ultimately to cirrhosis, which is generally apparent after many years. In some cases, those with cirrhosis will go on to develop liver failure or other complications, including liver cancer or life-threatening esophageal varices and gastric varices (**Ryan and Ray, 2004**).

Chronic hepatitis C is defined as infection with the hepatitis C virus persisting for more than six months based on the presence of its RNA. Chronic infections are typically without symptoms during the first few decades, and thus it is most commonly discovered following the investigation of elevated liver enzyme levels or during a routine screening of high risk individuals(**Kanwal and Bruce, 2011**).

Several immunologic abnormalities, such as production of autoantibodies, like cryoglobulins, are associated with HCV infection. Hepatitis C virus infection plays an

Introduction

important role in the pathogenesis of the immunologic derangement (**Boyer and Marcellin, 2000**).

Hepatitis C Virus infection frequently causes Organ-specific and non-specific autoantibodies (NOSA) were first described in autoimmune disorders, but many of them may also be found during other viral infections, Hepatitis C Virus (HCV) seems to be highly auto immunogenic because numerous autoantibodies have been detected in HCV-infected patients (**Chretien et al.,2009**) .

Antinuclear antibodies (ANA) and smooth muscle antibodies (SMA) are the most common non-organ-specific autoantibodies (NOSA) in patients with HCV related chronic liver disease (CLD) (**Peng et al .,2001**) .

Antinuclear antibody is one of the most frequently detected autoantibodies. The prevalence of ANA in HCV infected individuals ranges from 21% to 34%. Although ANA is the diagnostic hallmark of systemic lupus erythrematosus (SLE) and type 1 autoimmune hepatitis, its role in chronic HCV infection is unclear (**Peng et al., 2001**) .

The presence of serum ANA is associated with various factors including advancing age, genetic predisposition

environmental agents, oestrogen-androgen balance, chronic infection and neoplasm (Hsieh et al., 2008) .

In some studies ANA positivity had no observed effect on HCV clinical outcome. ANA positivity was associated with being in the group of patient exhibiting quicker progression of HCV fibrosis although this did not reach statistical significance . Associations of ANA positivity with non-response to therapy were not observed (Yee et al., 2004) .

AIM OF THE WORK

This work aims to study the frequency of occurrence of ANA in an Egyptian sample of patients with chronic hepatitis C virus infection as well its correlation with biochemical, histological and clinical features of the disease and their relation to antiviral therapy.