PREVALENCE OF ANTIPHOSPHOLIPID ANTIBODIES IN PATIENTS WITH CHRONIC HEPATITIS C IN CORRELATION WITH LIVER INJURY

Thesis Submitted in Partial Fulfillment of Master Degree in Internal Medicine

By

Mohamed Osama Aly Aly

M.B., B.Ch.

Under Supervision of

Professor Dr. Ahmed Shawky El sawaby

Professor of Internal Medicine and gastroenterology

Faculty of Medicine, Ain Shams University

Professor Dr. Mohamed Abdel Maboud Mohamed

Professor of Internal Medicine and gastroenterology

Faculty of Medicine, Ain Shams University

Dr.Sameh Ahmed Abdel-Bary

Lecturer of Internal Medicine

Faculty of Medicine, Ain Shams University

2009

Introduction

Antiphospholipd antibodies (APAs) are autoantibodies with an affinity to anionic phospholipids

They are organ nonspecific antibodies that have been reported in various clinical conditions such as deep venous thrombosis, arterial occlusive events (eg, stroke, myocardial infarction), and recurrent fetal loss and thrombocytopenia.

They are also associated with vasospastic phenomena such as migraine headache, Raynaud phenomenon, and transient ischemic attack (TIA). However, the pathogenesis and clinical significance of these antibodies are still unclear ***(Wilson et al., 1999).***

Also various infectious diseases can induce Antiphospholipid antibodies, Anticardiolipin antibodies (ACL) have been detected in various infectious diseases particularly of viral origin ,such as human immunodeficiency virus, hepatitis A and mumps ***(Mackworth-Young et al., 1991)(Mcneil,1992).***

These antibodies are not usually associated with thrombotic events, as happens with autoimmune diseases, in which these antibodies need the presence of β_2-glycoprotein I (β2GPI) which bears the epitope(s) for (ACL), **(*Cervera et al., 2003).***

There are several kinds of antiphospholipid antibodies. The two most commonly measured kinds are lupus anticoagulant (LA) and anticardiolipin antibody (ACL).Lupus anticoagulant and anticardiolipin antibody are closely related, but are not the same antibody. This means that a person can have one and not the other ***(Gharavi et al., 1990).***

For example, in various studies, 8% to 65 % of people with lupus have the lupus anticoagulant, and 25% to 61 % have anticardiolipin antibody. These antibodies can also be found in people who do not have lupus ***(Gharavi et al., 1990).***

There are other antiphospholipid antibodies, but they are not routinely measured. These include anti-beta 2 glycoprotein I, anti-prothrombin, the "false-positive" test for syphilis ***(Gharavi et al., 1990).***

The World Health Organization has declared hepatitis C a global health problem, with approximately 3% of the world's population (roughly 170-200 million people) infected with HCV. In the US, approximately 3 million people are chronically infected, many of whom are still undiagnosed. In Egypt the situation is quite worse, as The national prevalence rate of HCV antibody positivity has been estimated to be between 10-13% in 2002 and contains the highest prevalence of HCV in the world **(*Mohamed , 2004).***

Recently, the estimated prevalence rate in Egypt is about 15% ***(EMH, 2007)***

The mechanisms whereby HCV circumvents immune response and establishes persistent infection are currently undefined. It is well known that the specific immune response to any viral infection is primed by macrophages and dendritic cells that present viral proteins to B cells, helper T cells, and cytotoxic T cells. Progression to persistent infection and the immunologic mechanisms of liver injury are the consequence of complicated interactions between the virus and host. Identification of immunologic correlates of viral clearance may contribute to the development of an effective vaccine and better therapy for HCV infection. ***(Guidotti, 1999).***

Aim of the Work:

In the present study we aim to investigate the prevalence and clinical significance of antiphospholipid antibodies in chronic hepatitis C infection and their relationship with the disease progression.

بسم الله الرحمن الرحيم

(قَالُواْ سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا

عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ)

صدق الله العظيم

سورة البقرة

ACKNOWLEDGMENT

First and foremost, I thank **Allah,** who gave me the strength to accomplish this work.

Words cannot express my sincere gratitude and appreciation to **Prof. Dr. Ahmed Shawky El sawaby** ,professor of Internal Medicine& Gastroenterology, Faculty of Medicine Ain Shams university; I had the honor to work under his supervision, I appreciate his generous guidance, keen interest and precious time he offered me throughout his study. His scientific advices were kindly given to me and are beyond acknowledgment.

I would like to express my sincere indebtedness and profound gratitude to, **Dr. Mohamed Abdel-Maboud Mohamed** Assistant Professor of Internal Medicine & Gastroenterology, Faculty of Medicine , Ain Shams University, for his continuous guidance, valuable suggestions and keen supervision throughout the work.

I wish also to express my deep gratitude to **Dr.Sameh Ahmed Abdel-Bary ,** Lecturer of Internal Medicine, Faculty of Medicine, Ain Shams University,for his continuous support, valuable remarks meticulous supervision and for offering me much of his time and effort throughout this study.

List Of Abbreviations

ACL (aCL)	Anti cardiolipin antibodies
AFM	Atomic force microscopic
ANA	Anti nuclear antibodies
Anx A5	Annexin A 5
APC	Activated protein C
APL (aPL)	Anti phospholipid antibodies
APS	Anti phospholipid syndrome
ARF	Alternative reading frame
ARFP	Alternative reading frame protein
BAFF	B lymphocytes activating factor
b-DNA	Branched DNA
BVDV	Bovine viral diarrhea virus
CAR	Coxsackievirus and adenovirus receptor
CCN2	Cysteine-rich 61/connective tissue growth factor neuroblastoma overexpressed
CCP	anti-cyclic citrullinated peptide
CCR7	Chemokine (C-C motif) receptor 7 (mediator of EBV effects on B lymphocytes. This receptor is expressed in various lymphoid tissues and activates B and T lymphocytes)
CLDN1	Claudin- 1
CMV	Cytomegalo virus
CsA	Cyclosporine A
CTGF	Connective tissue growth factor
CYP2E1	Cytochrome P450 2E1 (involved in metabolism of xenobiotics)
DC	Dendritic cells
DC-SIGN	Dendritic cell-specific intercellular adhesion molecule-3 grabbing non integrin
EBV	Ebstein barr virus
EC	Endothelial cell
ECE	Endothelin converting enzyme
ET1	Endothelin-1
F	Frame shift
FGF	Fibroblast growth factor
FI	Fibrosis index
G1cNAc	N-acetyl-beta-glucosamine

GAG	Glycosaminoglycans
GBV-B	GB virus B (hepatotrophic virus closely related to HCV)
HAI	Hepatitis activity index
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HCVcc	HCV cell culture system
HCVpp	Hepatitis C virus pseudo particles
HGF	Hepatocyte growth factor
HIV	Human immunodeficiency virus
HNE	4-hydroxynonenal
HRP	Horseradish peroxidase
Huh-7	Human hepatoma cell line
ICAM-1	Intercellular adhesion molecule-1
IGF	Insulin-like growth factor
IRES	Internal ribosome entry site
IRF-3	Interferon regulatory factor 3
JAK-STAT	Janus kinases & Signal Transducers & Activators of Transcription
LA	Lupus anticoagulant
LDLR	Low density lipoprotein receptor
LKM	Anti liver kidney microsomal antibodies
LPs	lipopolysaccharides
L-SIGN	Liver /lymph node –specific intercellular adhesion molecule-3-grabbing integrin
MAPK	Mitogen-activated protein kinase
MC	Mixed cryoglobulinemia
MCP-1	Monocyte chemotactic peptide
MDC	Myeloid derived dendritic cells
MHC	Major histocompatibility complex
MMP-2	Matrix metalloproteinase-2
MPGN	Membrano proliferative glomerulonephritis
MT1-MMP	Membrane type 1 matrix metalloproteinase
NASH	Non-alchoholic steatohepatitis
NF-KB	Nuclear factor KB
NKs	Natural killer cells
NOSA	Non –organ specific antibodies
O.D	Optical density
ORF	Open reading frame
PBMCs	Peripheral blood mononuclear cells

PCT	Porphyria cutanea tarda
PDC	Plasmacytoid derived dendritic cells
PDGF	Platelet derived growth factor
PPARs	Peroxisomal proliferator activated receptors
PT	prothrombin
RA	Rheumatoid arthritis
RdRp	RNA dependent RNA polymerase
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SLE	Systemic lupus erythematosus
SMA	Anti smooth muscle antibodies
SR-BI	Scavenger receptor class B type I
TGF	Transforming growth factor
Th1 &Th2	T helper cells 1&2
TIMP	Tissue inhibitor of metalloproteinase.
TLR2	Toll like receptor 2
TMA	Transcription mediated amplification
TMB	Tetrmethylbenzidine
tPA	Tissue plasminogen activator
Tregs	Regulatory T cells
VDRL	Veneral disease research laboratory
VEGF	Vascular endothelial cell growth factor
β_2GPI	β_2 glycoprotein I

List Of Contents

List of Tables