Study of anticardiolipin antibodies in hepatitis C seropositive prevalent hemodialysis patients

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List of Abbreviations

ACA	anticardiolipin antibodies
acl	anticardiolipin antibodies
APC	Activated protein C
aPL	Phospholipid antibodies
apoER٢	apolipoprotein E receptor ٢
APS	anti-phospholipid syndrome
aPT	anti-prothrombin
AVF	arterio-venous fistula
AVG	arterio-venous grafts
B٢GPI	B٢-Glycoprotein I
bFV	bovine factor V
CAPS	catastrophic antiphospholipid Syndrome
CL	cardiolipin
CTLA-٤	cytotoxic T lymphocyte associated antigen ٤
C-X-C motif	chemokine
CXCL٤	ligand ٤
DOPPS	Dialysis Outcomes and Practice Patterns Study
ESRD	End stage renal disease
HBV	hepatitis B virus
HCV	Hepatitis C virus
HD	hemodialysis
HDL	High density lipoprotein
Hf II	human factor II
HITT	heparin-induced thrombocytopenia and thrombosis syndrome
HIV	human immunodeficiency virus
HO-١	Heme oxygenase-١
Ig	immunoglobulin
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M

LA	Lupus anticoagulant
LCMV	lymphocytic choriomeningitis virus
LDL	Low density lipoprotein
MAP	Mitogen-activated protein
MCII	mixed cryoglobulinemia type II
MI	myocardial infarction
MTHFR	The methylene tetrahydrofolate reductase
NAPS	nephropathy of APS
NHL	non-Hodgkin's B cell lymphomas
PAI-١	plasminogen activator of type ١
PAI-١	plasminogen activator inhibitor- ١
PAPS	primary APS
PCR	Polymerase chain reaction
PD-١	programmed cell death ١
PF٤	Platelet factor ٤
PGI٢	prostacyclin
PLs	phospholipids
PP	Pulse pressure
PS	phosphatidylserine
PTFE	polytetrafluoroethylene
Qa	Access flow
RFLP	restriction fragment length polymorphism
SLE	systemic lupus erythematosus
SS	Sjögren's syndrome
TGF- P ١	Transforming growth factor- p ١
Tim-٣	T cell immunogiobulin and mucin domain containing molecule ٣
TLR-٤	Toll-like receptor ٤
TNF-a	Tumor necrosis factor-a
t-PA	plasminogen tissue activator
TXA٢	thromboxane A٢
u-PA	urokinase plasminogen activator
VSMC	vascular smooth muscle cell
VDRL	Venereal Disease Research Laboratory test

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Dedication

To the soul of my father that I wish to be present at this time.

All honor to Allah and my mother that support me all through my way.

To my lovely wife, and my daughter Nour that light up our lives.

Introduction

Hepatitis C virus infection is a common problem in dialysis patients with the prevalence ranging from ١ to ٦٣٪. Long-term kidney disease, multiple blood transfusions and exposure to nosocomial infections are known risk factors for acquiring hepatitis C virus infection in hemodialysis patients. **(Peter Kes.٢٠٠٧)**

Vascular access failure is a major cause of morbidity in chronic hemodialysis patients where haemodialysis patient is critically dependent on the availability of adequate access to the systemic circulation, ideally via a native arteriovenous fistula. The Primary failure rate of an arteriovenous fistula ranges between ٢٠–٥٤٪, due to thrombosis or failure of maturation. **(Ashley Irish, et al. ٢٠٠٩)**

Infection with hepatitis C virus may lead to an auto-antibody response. It has been reported that chronically infected hepatitis C virus patients have anti-smooth muscle antibodies, rheumatoid factor, anti-liver-kidney-microsomal antibodies, anticardiolipin antibodies, and low titers of anti-nuclear antibodies. **(Joseph, et al. ٢٠٠٠)**

Anticardiolipin antibodies are a heterogeneous family of autoantibodies directed against protein-phospholipid complexes. Most anticardiolipin antibody immunoassays require B٢-glycoprotein-١ to react with anticardiolipin. The presence of these antibodies is one of laboratory diagnostic criteria for antiphospholipid syndromes characterized by venous and arterial thrombosis. **(Georg Endler, et al. ٢٠٠٦)**

Immunoglobulin-G anticardiolipin antibody is associated with venous and arterial thrombosis in patients with normal renal function. Previous investigations have reported the association of raised Immunoglobulin-G anticardiolipin antibody titer with recurrent vascular access thrombosis in hemodialysis patients. **(Lee CH, et al. ٢٠٠٦).**

The mechanism of anticardiolipin associated vasculopathy includes interaction of endothelium with platelets and antiphospholipid antibodies, to promote a cascade of reactions yielding recurrent local thromboses and intimal hyperplasia.

Platelet-endothelium interaction mediated by anticardiolipin may alter thromboxane A٢- prostacyclin

balance, leading to enhanced thrombosis and vasoconstriction. Patients with renal failure may be especially prone to this effect because uraemia is associated with the inhibition of nitric oxide synthase, and because of the effect of hypertension and advanced glycosylation end products on endothelial cell relaxation and proliferation, and on endothelin production. Endothelin-١ which induces vasospasm and arterial occlusion is released by endothelium in response to antiphospholipid antibodies. **(Y S Haviv. ٢٠٠٠)**

A second mechanism focuses on oxidant-mediated injury of the vascular endothelium. Oxidized low-density lipoprotein (LDL), a major contributor to atherosclerosis, is taken up by macrophages, leading to macrophage activation and subsequent damage to endothelial cells. Autoantibodies to oxidized LDL occur in association with anticardiolipin antibodies, and some anticardiolipin antibodies cross-react with oxidized LDL. Moreover, anticardiolipin antibodies bind to oxidized, but not reduced, cardiolipin, suggesting that anticardiolipin antibodies recognize oxidized phospholipids, phospholipid-binding proteins, or both. **(Jerrold S. ٢٠٠٧)**

Aim of the study:

The aim of study is to assess the frequency of anticardiolipin antibodies in hepatitis C seropositive prevalent hemodialysis patients and its possible relation to thrombotic effects including vascular access.

Antiphospholipid syndrome

Antiphospholipid antibodies (aPL) are a heterogeneous group of circulating immunoglobulins arising in a wide range of infectious and autoimmune diseases. Since the early ١٩٨٠s, the interest in anticardiolipin antibodies (aCL) has exponentially increased due to their association with thrombosis. The antiphospholipid syndrome (APS) was defined as a clinical disorder characterized by thrombosis and pregnancy morbidity associated to the persistent presence of aCL and/or lupus anticoagulant (LA).
(Khamashta MA, et al. ٢٠٠٦)

Antiphospholipid antibodies are directed against phospholipid–protein complexes or phospholipid-binding proteins, such as B٢- glycoprotein I (B٢GP I), prothrombin, protein C, protein S, thrombomodulin, annexin V, and kininogen. The term “antiphospholipid antibody” is therefore incorrect, because the antibody is actually directed against a phospholipid–protein complex, but the name has been retained for historical reasons. Although the negatively charged phospholipid cardiolipin plays the most important role, phosphatidylserine, phosphatidyl-ethanolamine, and phosphatidylcholine may

also form part of the complex. The target epitope is still not fully explained. **(Galli M. ٢٠٠٣)**

Table ( ) Antiphospholipid antibodies

Antibodies to anionic phospholipids
Cardiolipin
Phosphatidylserine
Phosphatidic acid
Phosphatidylinositol
Antibodies to neutral phospholipids
Phosphatidylcholine
Antibodies to zwitteronic phospholipids
Phosphatidylethanolamine
Antibodies to phospholipid binding proteins
B٢GPI
Prothrombin
Annexin V
Protein C
Protein S
Low molecular weight kininogens
High molecular weight kininogens

Maria L, et al.

Anticardiolipin antibodies:

Cardiolipin is very acidic, and composed of two molecules of phosphatidic acid joined together by Glycerol Bridge (diphosphatidyl-glycerol). Linoleic acid is the predominant fatty aid of diphosphatidylglycerol. Cardiolipin is found primarily in the inner membrane of mitochondria and bacterial cell membrane **(Hariss EN. ١٩٩٠)**

Cardiolipin is an anionic phospholipid, historically important as an antigen for testing reagin in syphilis serology. Currently, it is a part of the antigenic composition used in the VDRL tests along with lecithin and cholesterol. **(Maria L, et al. ٢٠١٠)**

In ١٩٨٣, Harris et al. developed a solid-phase radioimmunoassay to detect aCL using cardiolipin as antigen. This assay proved to be more sensitive than the classical VDRL test in detecting aPL. However, in addition to detecting aCL, this assay also detects antibodies to serum or plasma proteins that bind to cardiolipin coated to the plate, in particular, antibodies to B٢GPI (anti-B٢GPI). **(Maria L, et al. ٢٠١٠)**

Table ( ) Historical description of antiphospholipid antibodies

١٩٠٦ Wasserman reaction (reagin)
١٩٤١ Reagin binds cardiolipin
١٩٥٢ False-positive test for syphilis
١٩٥٢ Lupus anticoagulant (LA)
١٩٦٠s LA: association with thrombosis
١٩٧٠s LA: association with fetal loss
١٩٨٣ Anticardiolipin antibody (aCL)
١٩٨٠s Detailed description of anti phospholipid syndrome
١٩٩٠ Phospholipid binding proteins (B٢GPI)
١٩٩٠s Animal models for APS
١٩٩٩ Classification criteria for definite APS
٢٠٠٦ Classification criteria updated