

Clinical Relevance of Antiphospholipid Antibodies in Deep Venous Thrombosis

Thesis

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✍️ *Noha Salah Abd El-Meguid Abo Shanab*

List of Contents

Subject	Page No.
List of Abbreviations.....	i
List of Tables.....	v
List of Figures	vii
Introduction	1
Aim of the Work.....	3
Review of Literature	
Chapter (1): Definition and Epidemiology	4
Chapter (2): Pathogenesis of Antiphospholipid Syndrome....	5
Chapter (3): Clinical Presentation of APS	26
Chapter (4): Diagnosis of Antiphospholipid Syndrome.....	35
Chapter (5): Evaluation of Laboratory Tests for APS	45
Chapter (6): Treatment of Antiphospholipid Syndrome	76
Subjects and Methods	79
Results.....	100
Discussion	125
Summary	135
Conclusion.....	138
Recommendations	139
References	140
Arabic Summary	—

List of Abbreviations

<i>Abbrev.</i>	<i>Meaning</i>
ACL	: Anticardiolipin
APA	: Antiphospholipid Antibodies
APL	: Antiphospholipid antibodies
APLN	: APL-Associated Nephropathy
APS	: Antiphospholipid Syndrome
APTT	: Activated Partial Thromboplastin Time
BCR	: B-Cell Receptor
CAPS	: Catastrophic Antiphospholipid Syndrome
CD	: Cluster of Differentiation
CL	: Cardiolipin
CV	: Coefficient of Variation
DA	: Diagnostic Accuracy
DCs	: Dendritic Cells
dPT	: Dilute Prothrombin Time
dRVVT	: Dilute Russell Viper Venom Time
DVT	: Deep Venous Thrombosis
EBV	: Epstein Barr Virus
EC	: Endothelial Cell
EIA	: Enzyme Immuno Assay
ELISA	: Enzyme Linked Immunosorbent Assay
F	: Factor
FN	: False Negative
FP	: False Positive
GP	: Glycoprotein
GPL	: IgG phospholipid unit
HELLP	: Hemolysis, Elevated Liver enzymes, Low Platelet levels
HLA	: Human Leukocyte Antigen

HUS	: Hemolytic-Uremic Syndrome
HUVECs	: Human Umbilical Vein Endothelial Cells
ICAM	: Intercellular Adhesion Molecule
Ig	: Immunoglobulin
INR	: International Normalized Ratio
IQR	: Inter Quartile Range
ISTH	: International Society of Thrombosis and Hemostasis
IUGR	: Intrauterine Growth Retardation
IVIG	: Intra Venous Immunoglobulins
K	: Kappa
KCT	: Kaolin Clotting Time
LA	: Lupus Anticoagulant
LDL	: Low Density Lipoprotein
LMWH	: Low Molecular Weight Heparin
MAPK	: Mitogen Activated Protein Kinases
MRI	: Magnetic Resonance Imaging
mRNA	: Messenger Ribonucleic Acid
MyD88	: Myeloid Differentiation Primary Response
NF	: Nuclear Factor
NPV	: Negative Predictive Value
NYHA	: New York Heart Association
PAI	: Plasminogen Activator Inhibitor
PC	: Phosphotidyl choline
PG	: Phophatidyl glycerol
PL	: Phospholipids
PNP	: Pooled Normal Plasma
PPP	: Platelet poor plasma
PPV	: Positive Predictive Value
PS	: Phosphatidylserine
PT	: Prothrombin/Time
RVV	: Russell Viper Venom

SCT	: Silica Clotting Time
SD	: Standard Deviation
Sens	: Sensitivity
SGU	: Standard G units
SLE	: Systemic Lupus Erythematosus
Spec	: Specificity
TF	: Tissue factor
Th1	: T Helper 1
TLR	: Toll Like Receptor
TN	: True Negative
TP	: True Positive
tPA	: Tissue Plasminogen Activator
TRAF6	: TNF Receptor Associated Factor 6
TT	: Thrombin Time
TXB2	: Thromboxane B2
TTP	: Thrombotic thrombocytopenic purpura
VCAM	: Vascular Cell Adhesion Molecule
VKA	: Vitamin K Antagonist
VTE	: Venous Thromboembolism
vWF	: von Willebrand Factor
β₂GPI	: β ₂ -glycoprotein I

List of Tables

Table No.	Title	Page No.
Table (1):	The Effects of APL Antibodies on Endothelial Cells	15
Table (2):	Clinical Manifestations of Antiphospholipid Antibodies	34
Table (3):	Revised Classification Criteria for Antiphospholipid Syndrome.....	40
Table (4):	Comparison of Laboratory Criteria of APS. ...	41
Table (5):	Calculation of the Percentage Correction for 4:1 APTT Mixing Studies:	51
Table (6):	Interpretation of Activated Partial Thromboplastin Time Mixing Studies in specimens without Heparin	51
Table (7):	Recommendations of the subcommittee for the Optimal Laboratory Detection of Lupus Anticoagulant (LA).	52
Table (8):	Cut-off values for Lupus Anticoagulant (LA) Detection	54
Table (9):	Management of non-obstetric APS complications.....	76
Table (10):	Management of obstetric APS complications.....	77
Table (11):	Performance characteristics of APTT-LA kit.....	85
Table (12):	Reproducibility of dRVVT kit	88
Table (13):	Precision of ACL kit.....	94

List of Tables *(Cont.)*

Table No.	Title	Page No.
Table (14):	Precision and reproducibility of β_2 GPI kit.....	97
Table (15):	Kappa index.....	99
Table (16):	Patients results.....	105
Table (17):	Patients' Results Interpretation.....	107
Table (18):	Characteristics of all studied patients.....	108
Table (19):	Agreement study between Antibody Based Assays and LA Coagulation Based Assays...	109
Table (20):	Agreement study between LA Coagulation Based Assays.....	110
Table (21):	Agreement study between ACL IgG & β_2 GPI IgG.....	111
Table (22):	Correlation between age & laboratory investigations.....	111
Table (23):	Correlation between numbers of attacks of DVT & laboratory Investigations.....	112
Table (24):	Correlation between coagulation based assay and antibody detection based assay.....	113
Table (25):	Comparison between patients with single attack of DVT and patients with recurrent attacks.....	114
Table (26):	Performance of laboratory tests in relation to final diagnosis of positive patients.....	116
Table (27):	Frequency of positive tests among patients ..	116

List of Figures

Figure No.	Title	Page No.
Figure (1):	β_2 GPI structure. Sushi domains are numbered 1 – 5.....	6
Figure (2):	Anti-prothrombin antibodies	7
Figure (3):	Schematic representation of the hypothesis that anti β_2 GPI Abs in complex with β_2 GPI may be able to amplify the production of autoantibodies via their ability to bind and crosslink TLR4	10
Figure (4):	Mechanism of Thrombosis	12
Figure (5):	Endothelial Cell Activation by Anti- β_2 GPI Autoantibodies.	16
Figure (6):	Pathogenic Clotting Mechanisms Mediated by APL	17
Figure (7):	The stable trimolecular complexes formed by APL with β_2 GI at the PL surface interfere with the proper assembly of the prothrombinase complex.....	18
Figure (8):	The coagulation pathways. Asterisks indicate potential sites of action of antibodies in APS.....	19
Figure (9):	Protein C Pathway.....	20
Figure (10):	(A): Protein S Activates Protein C, (B): Anti β_2 GPI/ β_2 GPI complexes prevent APC/Va/VIIIa complexes for binding to phospholipids or even prevent the formation of these complexes	21

List of Figures (Cont.)

Figure No.	Title	Page No.
Figure (11):	The Fibrinolytic Pathway.....	22
Figure (12):	Steps of mixing study 1:1	50
Figure (13):	Rosner index and Percent Formulae	50
Figure (14):	Antiphospholipid antibody determination by dRVVT.....	64
Figure (15):	β_2 Glycoprotein structure where it consists of five domains from I-V.	70
Figure (16):	Model of cell activation by autoantibodies against β_2 GPI.....	71
Figure (17):	Schematic representation of the cardiolipin ELISA, which detects a number of antibody specificities, including β_2 GPI.....	72
Figure (18):	Antiphospholipid antibody determination by ELISA	73
Figure (19):	Percentage of patients with single and recurrent attacks of DVT	117
Figure (20):	Positive and negative laboratory investigations	117
Figure (21):	Agreement study between ACL IgG and other laboratory investigations	118
Figure (22):	Agreement study between β_2 GPI IgG and other laboratory investigations.....	118

List of Figures *(Cont.)*

Figure No.	Title	Page No.
Figure (23):	Agreement study between APTT-LA and dRVVT screen ratio and dRVVT correction ratio	119
Figure (24):	Agreement study between Rosner index and dRVVT screen ratio and dRVVT correction ratio	119
Figure (25):	Agreement study between ACL IgG and β_2 GPI IgG.....	120
Figure (26):	Scatter significant correlation between age and ACL IgG	121
Figure (27):	Scatter significant correlation between age and Rosner index	121
Figure (28):	Scatter significant correlation between number of DVT attacks and ACL IgG	122
Figure (29):	Scatter significant correlation between number of DVT attacks and Rosner index.....	122
Figure (30):	Scatter significant correlation between ACL IgG and dRVVT screen ratio	123
Figure (31):	Scatter significant correlation between ACL IgG and dRVVT confirm correction ratio	123
Figure (32):	Comparison between Patients with single attack of DVT and patients with recurrent attacks.	124

Introduction

Antiphospholipid syndrome (APS) is an immune-mediated, acquired thrombophilia characterized by arterial or venous thrombosis, in association with persistently elevated levels of antiphospholipid (APA) antibodies (*Sikara et al., 2010*).

The most common type of venous thrombosis associated with APS is lower extremity deep venous thrombosis (DVT) (*Farmer-Boat Wright and Roubey, 2009*).

Antiphospholipid antibodies such as lupus anticoagulant (LA) and anticardiolipin antibody (ACL) are associated with a hypercoagulable state manifested by arterial/venous thrombosis, which may cause cerebral infarction, central retinal arterial/venous occlusion, myocardial infarction, pulmonary infarction, mesenteric arterial/venous occlusion, habitual abortion, and arterial/venous occlusion and ulceration in four limbs (*Kinuya et al., 2001*).

Lupus anticoagulant antibodies are members of the heterogenous family of antiphospholipid antibodies, whose specificity, initially believed to be directed towards negatively charged phospholipids (*De Groot and Derksen, 2004*), other antiphospholipid antibodies are annexin V, high and low molecular weight kininogens and factor XI (*Triplett, 2000*).

β_2 GPI is a highly glycosylated single-chain protein that is present in plasma without known physiological function. The protein avidly binds to negatively charged phospholipids such as cardiolipin (CL), phosphatidyl serine (PS) or phosphatidyl inositol (PI). Upon phospholipid binding, β_2 GPI changes conformation and exposes a cryptic epitope to which high affinity antibodies can bind (**De Laat et al., 2006**).

Multiple screening tests are recommended (e.g., APTT, dilute PT and dilute Russell viper venom time (dRVVT). dRVVT is one of the most important screening procedures. In many instances, commercially available dRVVT systems include a screening reagent with low phospholipid concentration (PL) and a confirmatory product with high PL concentration (**Triplett, 2000**).



Aim of the Work

The aim of this study is to determine the frequency of positive antiphospholipid antibody syndrome detected by laboratory investigations with unexplained DVT.

Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by arterial and/or venous thrombosis, fetal death, recurrent miscarriages, and thrombocytopenia, along with elevated titers of antiphospholipid antibody (APA): lupus anticoagulant (LA) and/or cardiolipin (CL) (*Gu et al., 2014*).

Epidemiology of APS:

Antiphospholipid syndrome (APS) is an important thrombophilic condition because it is of high prevalence and is associated with considerable morbidity and mortality (*Gómez-Puerta and Cervera, 2014*).

Antiphospholipid antibodies (APL) accounts for a significant proportion of thrombosis in the general population up to 20% of idiopathic deep venous thrombosis (DVT) patients are APL positive. Anticardiolipin (ACL) is predictive of DVT and pulmonary embolism in the general population (*Nalli et al., 2014*).

Anticardiolipin antibodies (ACL) are seen in the general population. Prevalencies 2 to 4% and they are usually low in titer and more common in the elderly. The strength of the association between aPL and thrombosis varies, depending on both the aPL tested and the populations studied. Titer and isotype are important: immunoglobulin Ig G ACL is more strongly associated with clinical events than IgM ACL, and the risk of thrombosis increases with higher titers. IgA ACL and low titers of IgG and IgM ACL are less frequently associated with complications (*Godfrey and D'Cruze, 2000*).