Clinical Relevance of Antiphospholipid Antibodies in Deep Venous Thrombosis

Thesis

Submitted for partial fulfillment of the MD Degree
In Clinical and Chemical Pathology

By

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2015

Acknowledgement

"First And Foremost, Thanks to **ALLAH**, Who granted me the power to accomplish this work.

I wish to express my deep gratitude and respect to **Professor Dr. Hanaa Mohamed Affify,** Professor of Clinical and Chemical Pathology, Faculty of Medicine, Ain Shams University. I would like to thank her for the patience and sincerity to instruct me through the work, I am also so grateful for the precious time she offered me. I would like to thank her for the great help, her incessant valuable support and guidance.

I would like to express my thanks and gratitude to **Professor Dr. Mona Ahmed Ismail,** Professor of Clinical and Chemical Pathology, Faculty of Medicine, Ain Shams University For her supervision, help, advice and her scientific generosity contributed a lot to the final shape of this work.

Also, I would like to express my deepest thanks and gratitude to **Doctor Abeer Attia Saad,** Assistant Prof. of Clinical and Chemical Pathology, Faculty of Medicine, Ain Shams University, for her help, assistance, advice and her efforts in helping me.

Also, I would like to express my feelings of great respect and deep gratitude to **Dr. Doaa Ahmed Gamal Eissa,** Assistant Professor of Clinical and Chemical Pathology, Faculty of Medicine, Ain Shams University. I would like to thank her for carrying the burden to closely observe, discuss, and evaluate this thesis; her comments during writing the thesis were so helpful in keeping me to the point. I would like to thank her for the precious instructions, and her kind sympathy.

I wish also to express my profound gratitude to **Dr. Sherif Mohamed Essam El-Din,** Assistant Prof. of General and Vascular Surgery, Faculty of Medicine, Ain Shams University, for his helpful guidance, encouragement and continuous advice.

Last but not least, I really owe my family and friends much more than words for making me able to trust my capabilities and together with their encouragement I was able to accomplish my work, for them no words of praise or gratitude are sufficient. At the end I would like to dedicate this thesis to the memory of my mother, I wish I fulfilled her dream.

Noha Salah Abd El-Megiud Abo Shanab

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List of Abbreviations

Abbrev.	Meaning
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	: Epstien 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
β_2GPI	: β_2-glycoprotein I

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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_2GPI 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_2GPI 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 anti-phospholipid 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).***