Study On Anticardiolipin Antibodies In Primary Vascular Occlusion

Thesis
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The M.Sc. Degree of **Internal Medicine**

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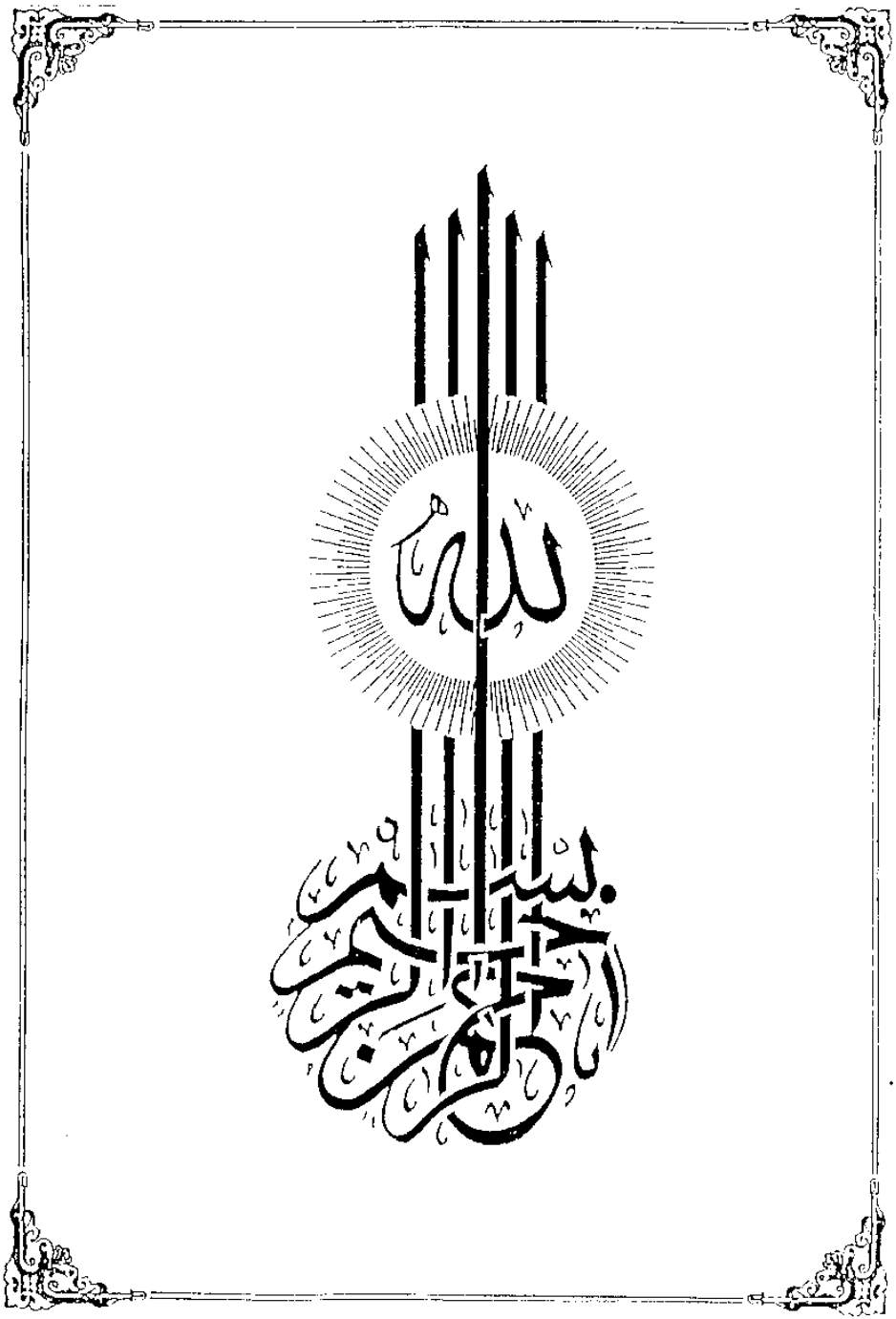
وفي الأرض آيات للموقنين

صدق الله العظيم



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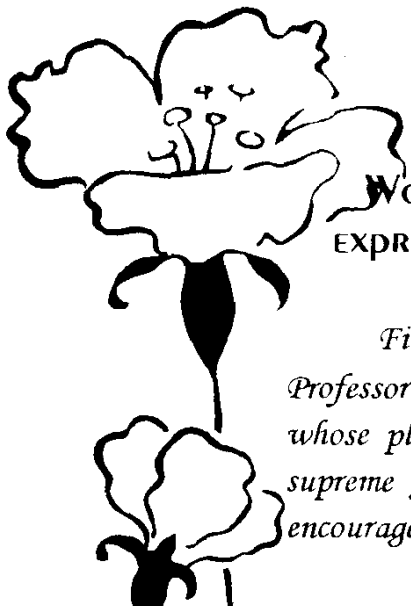

WORDS STAND SHORT WHEN THEY COME TO EXPRESS MY GRATEFULNESS TO MY SUPERVISORS,

First, to start with **Prof. Dr. Omar Fathy,** *Professor of Internal Medicine, Ain-Shams University whose place can only be first, he has been of utmost supreme guidance and supervision with the most kind encouragement..*

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H. Fathey

Dedication

To whom I owe so much beyond words,
To GOD,
who gave me the mind, power, and capability

To my father's soul, who has endowed me with ulterior aegis

To my mother, who has been my auric aura

And last, but by far least, to my husband and my son Omar who have and will always be the source of inspiration for all my endeavorous auspices.

H. Fathey

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List of abbreviations

Abbreviation	Full name
ACA	Anticardiolipin antibodies
ADP	Adenosine diphosphate
APA	Antiphospholipid antibodies
APS	Antiphospholipid syndrome
β_2 GP-I	Beta 2 glycoprotein I
CVS	Cerebrovascular stroke
DVT	Deep vein thrombosis
HRP	Horse redish peroxidase
INR	International normalized ratio
LAC	Lupus anticoagulant
MI	Myocardial infarction
PAN	Polyarteritis nodosa
PPP	Platelet poor plasma
PRP	Platelet rich plasma
SLE	Systemic lupus erythematosus
t-PA	Tissue plasminogen activator

Introduction and Aim of work

Anticardiolipin Antibodies in Primary Vascular Occlusion

Introduction :-

Various clinical conditions are associated with vascular occlusion with or without thrombophilia. It is only within recent years that the physiological and clinical importance of blood coagulation inhibitors has become appreciated.

Anticardiolipin antibodies have been found to be associated with diverse clinical manifestations related to intravascular phenomena as well as those related to cell damage. They are associated with thrombotic manifestations occurring in course of autoimmune and non autoimmune diseases as well as few studies in primary anticardiolipin syndrome with tendency to recurrent thrombosis, recurrent abortion, thrombocytopenia, hemolytic anemia, and neurological diseases.

Different isotypes are associated with clinical manifestations including IgG, IgM, and IgA immunoglobulin subclasses. Therefore, the role of anticardiolipin antibodies in patients with recurrent primary vascular occlusive clinical conditions that are not the result of local cause or systemic disease remains to be established, in order to assess their relation to the hemostatic disturbances observed in those patients.

Aim of the work :-

The aim of the study is the determination of anticardiolipin antibodies and platelet aggregation with ADP in patients with primary vascular occlusion, in an attempt to study the relation between them and their impact on disease status.

Review of Literature

Blood Coagulation Cascade

The coagulation mechanism is composed of a series of reactions which functions as a biological amplifier. This view was enunciated by ***MacFarlane, (1964)*** and ***Davie and Ratnoff, (1964)*** and termed cascade hypothesis.

The coagulation mechanism is concerned with the formation of thrombin which converts fibrinogen into soluble fibrin allowing stabilization of the aggregated platelets at the site of injury. Thirteen coagulation factors circulate in the plasma in their inactive forms (zymogens) ***(Jandle, 1987).***

Each zymogen is converted into an active coagulation factor (enzyme) and this in turn activate the next zymogen in the sequence. With each step in this coagulation sequence, the system is amplified to produce increasing numbers of activated coagulation molecules culminating in the generation of thrombin, the enzyme that convert fibrinogen into fibrin ***(Davie et al., 1980).*** Thrombin is also a potent stimulator of platelet aggregation, it also activates procofactors, factor V and factor VIII to active cofactors and activates factor XIII, which catalyzes the formation of a stable, covalently cross-linked fibrin clot ***(Ofosu et al., 1989).*** The coagulation process follows either an extrinsic or an intrinsic one.

Vascular injury leads to activation of both systems, the extrinsic pathway by providing tissue factors, and intrinsic pathway by providing a foreign substance for activation of Hageman factor ***(Williams et al., 1983).***

1- The contact activation system (intrinsic pathway):-

It is composed of factor XII, prekallikrein, high molecular weight kininogen, and factor XI, the interaction of which leads to the conversion of factor XII to factor XIIa which proteolytically activates factor IX to factor IXa which in the presence of thrombin modified factor VIIIa, Ca^{++} and negatively charged phospholipids, activates factor X leading to the formation of prothrombinase complex which converts prothrombin to thrombin with subsequent clot formation ***(Nemerson, 1988).***

The precise mechanism for initiation of contact system has remained obscure and neither the mechanism for accelerating effect of an anionic surface nor the mechanism for initial activation of factor XII has been established ***(Kaplan and Silverberg, 1987).***

The earliest phase of the intrinsic pathway is slow, but once thrombin is generated, the process is greatly accelerated as thrombin potentiates the activation of factor V, VIII and thrombin itself. Thrombin also induce platelet aggregation and increases the availability of platelet factor III. Interestingly, thrombin destroys factor V and VIII by protein C activation after potentiating their effects. In this way, fibrin formation is stopped when a high concentration of thrombin has been achieved. So, actually, it is a feed-back mechanism ***(Williams eet al., 1983).***

Tissue factor dependent coagulation system (extrinsic pathway):-

Involves the formation of a complex compound of factor VII associated with the membrane bound tissue factor in the presence of Ca^{++}. The association of tissue factor with factor VII nay be the crucial reaction in initiation of coagulation following both factors X and IX. So, in tissue factor initiated coagulation, factor Xa is generated directly by the action of tissue factor, factor VIIa complex, and indirectly by the simultaneous activation of factor IX. The instantaneous concentration of factor Xa is determined by the summation of the two pathways ***(Nemerson, 1988).***

Common pathway :-

Factor Xa generated through both routs is identical. Activated factor X forms a complex with platelet factor III, Ca^{++}, and an accelerator or coenzyme (factor V) converting prothrombin to thrombin ***(Biggs, 1980).*** Thrombin is a protease that converts fibrinogen to fibrin providing stability to the hemostatic plug of platelets ***(Hirsh and Branin, 1983).***

The newly formed fibrin clots are ineffective hemostatically, being susceptible to lysis by plasmin and other proteolytic enzymes unless cross-linked by factor XIIIa generated through activation of thrombin. In the presence of Ca^{++}, factor XIIIa forms cross links between the outer ends of fibrin molecules by replacing the NH_2 of a glutamine of one of its constituents with E. amino group of lysine in an adjacent chain. The shown cross linking of α2-antiplasmin to fibrin probably explains the relative resistance of clots formed in plasma against plasmin digestion ***(Kaczmaek et al., 1988).***

Hemostatic control mechanisms of blood coagulation :-

The hemostatic control mechanisms of blood coagulation act as counter factor of equal potency to coagulation mechanism aiming at limiting the hemostatic plug to desirable size and neutralizing the active procoagulants that may enter the general circulation ***(Haley et al., 1989).***

Normally, thrombogenesis is modulated by several efficient protective mechanisms. These include; the normal intact endothelium, the inhibitors of activated coagulation factors, hepatic clearance of activated coagulation factors, the fibrinolytic system, and dilution of activated coagulation factors by the effects of blood flow ***(Haley et al., 1989).***

1- Non thrombogenic properties of endothelial cells :-

Vascular endothelium is non thrombogenic to flowing blood ***(Rosenberg, 1984).*** Endothelial cell surface glycosaminoglycans and thrombomodulin are potent inhibitors of coagulation, while vessel wall generation of prostacyclin and nitric oxide, and plasminogen activators limit platelet aggregation and fibrin deposition, respectively ***(Myers et al., 1990).***

Thrombomodulin and heparan sulfate present on the surface of normal endothelium are important modulators of thrombin activity ***(Esmon et al., 1982).*** The substrate specificity for thrombin changes markedly when it complexes with thrombomodulin ***(Owen et al., 1982)*** after binding