Platelet Glycoprotein IIb IIIa Polymorphism and Sticky Platelets in Acute Coronary Syndrome

Thesis

Submitted in the fulfilment of the M.D. degree in Internal Medicine

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2010

Dedication

I dedicate this work to Dr. Alaa Mahmoud Abd El Rahman, God bless his soul, he was one of the best, he left us on 23/8/2007, but an endless love and respect will always remain.

Acknowledgment

FIRST OF ALL THANK GOD for all his blessings and giving, especially the blessing of being surrounded by loving family, they give me unconditional love and support in every way possible throughout this work and beyond.

I would like to express my very great appreciation to **Prof. Dr. Mona M. El-Kassass,** Professor of Internal Medicine, Cairo University. I am truly obliged for her kindness, maternal compassion, constant support and guidance. I sincerely value the time and effort she has given to this work.

I would like also to thank **Prof. Dr. Usama Ahmed Khalaf Allah**, Professor of Clinical Pathology, Cairo University, for giving me the opportunity to carry out most of the practical work of this study and for his constant guidance.

I would like to acknowledge and extend my heartfelt gratitude to the following persons: **Prof. Dr. Hadi Goubran**; professor of internal medicine, Cairo University, **Prof. Dr. Sherif Naseh Amin**; Professor of Clinical Pathology, Cairo University, and **Prof. Dr. Khaled Souror**; Professor and head of cardiology department, Cairo University. They have made the completion of this work possible.

Finally, I would like to extend my thanks to all the staff members and colleagues of Clinical hematology department, Faculty of Medicine, Cairo University, for their constant motivation and support.

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List of Abbreviations

ACC	American Colleague Of Cardiology.
ACS	Acute Coronary Syndrome.
ACT	Activated Clotting Time.
ADMIDAS	Adjacent to The MIDAS.
ADP	Adenine Diphosphate.
AHA	American Heart Association.
AIT	Alloimmune Thrombocytopenia.
AMI	Acute Myocardial Infarction.
APTT	Activated Partial Thromboplastine Time.
AST	Aspartate Transaminase.
BNP	Brain Natriuretic Peptide.
CABG	Coronary Artery Bypass Graft.
CAD	Coronary Artery Disease.
CHD	Coronary Heart Disease.
CK	Creatine Kinase.
CK-MB	Creatine Kinase- Myocardial Band.
COX	Cyclo-Oxygense.
CrCl	Creatinine Clearance.
CRP	C-Reactive Protein.
CT	Computed Tomography.
DAG	Diacyle Glycerol.
DDAVP	Desmopressin (1-desamino-8-D-arginine vasopressin).
DMS	Demarcation Membrane System.
DTIs	Direct Thrombin Inhibitors.
EGF	Epidermal Growth Factor.
FOG	Friend Of GATA1.
GFR	Glomerular Filtration Rate.
GP	Glycoprotein.

GRACE	Global Registry of Acute Coronary Events.
HDL	High Density Lipoprotein.
HIT	Heparin Induced Thrombocytopenia.
Hs CRP	Highly Sensitive C-Reactive Protein.
HSC	Hematopoietic Stem Cell.
HUS	Hemolytic Uremic Syndrome.
ICSH/ISLH	International Council for Standardization in Haematology/ International Society for Laboratory Hematology
IP3	Inositol Triphosphate.
ITGβ3	Integrine β3.
LBBB	Left Bundle-Branch Block.
LDH	Lactate Dehydrogenase.
LDL	Low Density Lipoprotein.
LIMBS	Ligand-Induced Metal Binding Site.
LMWHs	Low-Molecular-Weight Heparin.
LTA	Light Transmission Agreggometry.
MDRD	Modification of Diet in Renal Disease.
MHC	Major Histocompatibility Complex.
MK	Megakaryocyte.
MoAbs	Monoclonal Antibodies.
MRI	Magnetic Resonance Image.
NSTEMI	Non-ST Segment Elevation Myocardial Infarction.
NT-proBNP	N-Terminal Pro-BNP.
OR	Odds Ratio.
PAD	Peripheral Arterial Disease.
PAR	Protease-Activated Receptor.
PCI	Percutaneous Coronary Intervention.
PFA-100®	Platelet Function Analyzer-100®.
PG	Prostaglandin.
PLC	Phospholipase C.

PPACK	D-Phenylalanyl-1-Prolyl-1 Arginine Chloromethyl Ketone
PRP	Platelet Rich Plasma
PRU	P2Y12 Reaction Units
PSI	Plexin-Semaphorin-Integrin.
STEMI	ST Segment Elevation Infarction
TIA	Transient Ischemic Attack.
TIMI	Thrombolysis In Myocardial Infarction.
Tnc	Troponine C.
TnI	Troponine I.
TnT	Troponin T.
TTP	Thrombotic Thrombocytopenic Purpura.
TXA2	Thromboxane A2.
UA	Unstable Angina.
UFH	Unfractionated Heparin.
VASP	Vasodilator Stimulated Phosphoprotein.
vWF	von Willebrand Factor.

Abstract

Background: ACS remains a leading cause of death and disability. Platelet activation is a hallmark of ACS. Numerous lines of evidence suggest a mechanistic link between platelet hyper-function and myocardial damage in patients with ACS. Platelet GP IIb IIIa plays an important role in platelet aggregation and adhesion. Genetic polymorphism of that receptor was found to be associated with increase the risk of myocardial infarction and sudden cardiac death.

Objectives: The aim of our study was to investigate the prevalence of various allelic forms of the Pl^{A} GPIIIa polymorphism in patients with ACS and whether it affects platelet reactivity.

Methods: The present work constitutes a study on 40 patients presenting with ACS and 10 age and sex matched healthy volunteers, all subjects were genotyped using PCR-RFLP technique and their platelet reactivity was evaluated under high shear stress using Impact- R cone and plate-let analyzer device.

Results: The Pl^{A2} carriers were 47.5% in ACS patients compared to 20% in the control group. The distribution of Pl^{A2} amongst patients with STEMI, NSTEMI and UA was 52.9%, 44.4% and 42.9% respectively. Also indices of platelet reactivity were higher in patients, especially those presenting with STEMI, than in healthy control and in carriers of Pl^{A2} allele than in non carriers. However, these differences did not reach statistical significance probably due to small number of subjects included in the study.

Conclusion: The prevalence Pl^{A2} allele in the Egyptian population seems to be high compared to other ethnic groups, The role of Pl^{A} genetic polymorphism as genetic determinant of CHD and its effect on platelet reactivity need to be further evaluated in larger studies.

Keywords: ACS/ Glycoprotein IIIa Polymorphism/platelet hyperreactivity.

INTRODUCTION

Probably the earliest clinico–pathologic correlation of coronary disease was recorded by Bonetus in 1700, in an overweight middle-aged poet who died a few minutes after "distress in breathing." The autopsy showed calcified occluded coronary arteries. However the first classical clinical variable and complex description of obstructed coronary disease is the hallmark paper submitted by Herrick in 1912. Indeed, he noted 28 different conditions that he had mistaken for coronary thrombosis (Herrick 1912).

Advances in the prevention, diagnosis, and treatment of acute myocardial infarction (AMI) and acute coronary syndrome (ACS) have been remarkable since the mid-20th century. Even the clinical terminology used to describe some of the various components of ACS have undergone change, while the latter term itself represents a fairly recent addition to the medical lexicon. Although there have been dramatic changes in diagnostic and therapeutic interventions used and impressive declines in morbidity and mortality, the differential diagnosis and complications of AMI and ACS remain as challenging now as they were half century ago (Malach and Imperato 2006).

EPIDEMIOLOGY

Coronary heart disease is a worldwide health epidemic. Thirty percent of all deaths worldwide can be attributed to cardiovascular disease, of which more than half are caused by CHD, and the forecasts for the future estimate a growing number as a consequence of lifestyle changes in developing countries. Globally, of those dying from cardiovascular diseases, 80 percent are in developing countries and not in Western world (Fuster et al., 2008).

Investigating the data of 7,733 participants in the Framingham Heart Study, Lloyd-Jones et al. (1999) demonstrated that lifetime risks of initial coronary events after age 40 is 49% for men and 32% for women.

DEFINITIONS

The term acute coronary syndrome refers to a range of acute myocardial ischemic states. It encompasses unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation infarction (STEMI). The leading symptom that initiates the diagnostic and therapeutic cascade is chest pain, but the classification of patients is based on electrocardiogram. Two categories of patients may be encountered (Fuster et al., 2008):

Patients with typical acute chest pain and persistent (>20 min) ST-segment elevation.

This is termed ST-elevation ACS (STE-ACS) and generally reflects an acute total coronary occlusion. Most of these patients will ultimately develop an ST-elevation MI (STEMI).

Patients with acute chest pain but without persistent ST-segment elevation.

They have rather persistent or transient ST-segment depression or T-wave inversion, flat T-waves, pseudo-normalization of T-waves, or no ECG changes at presentation. At presentation, the working diagnosis of non-STE-ACS (NSTE-ACS), based on the measurement of troponins, will be further qualified into non-ST elevation MI (NSTEMI) or unstable angina (UA).

PATHOPHYSIOLOGY

ACS represent a life-threatening manifestation of atherosclerosis usually precipitated by acute thrombosis, induced by a ruptured or eroded atherosclerotic plaque, with or without concomitant vasoconstriction, causing a sudden and critical reduction in blood flow. In the complex process of plaque disruption, inflammation was revealed as a key pathophysiological element (Fuster et al., 2008).

In rare cases, ACS may have a non-atherosclerotic aetiology such as arteritis, trauma, dissection, thrombo-embolism, congenital anomalies, cocaine abuse, and complications of cardiac catheterization (Fuster et al., 2008).

Atherosclerosis is a chronic, multifocal immunoinflammatory, fibro-proliferative disease of medium-sized and large arteries mainly driven by lipid accumulation. The development of atherosclerosis appears to follow a complex pathway (Falk 2006):

Endothelial dysfunction is caused by a number of factors such as cigarette smoking, hypertension, and hyperlipidemia. This permits entry of various blood components into the arterial intimal layer. These components ordinarily roll along the endothelial layer and do not damage the artery. Infiltration of leukocytes, lipids (carried by LDL particles), and macrophages takes places as these blood cells accumulate within the intimal layer of the artery.

Inflammation occurs, and lipid-rich foam cells form as macrophages ingest LDL particles. These foam cells accumulate and grow into fatty streaks, which eventually bulge out into the arterial lumen. The disease may still be reversible at this stage if LDL cholesterol levels in the blood are decreased, HDL particles increased, and endothelial function restored.

Proliferation and migration of smooth muscle cells from the medial layer form a fibrous cap over the fatty lesion. This is now a complex lesion that is not entirely reversible. Proliferation of the vasovasorum provides the lesion with its own blood supply.

Continued plaque progression is characterized by growth and eventual necrosis of the lipid core, calcification, hemorrhage within the plaque, and surface erosion with formation of nonobstructive clots. The external elastic lamina may stretch to accommodate this plaque growth without the development of ischemia, but eventually the arterial lumen may narrow to the extent that ischemia may develop during periods of physical or psychological stress. This ischemia may be silent or cause angina.

Thinning and weakening of the fibrous cap due to the action of matrix metalloproteinases released from macrophages, coupled with the shear stress of blood flow over the luminal surface of the plaque may cause acute plaque rupture. Precipitating factors like nicotine use, excessive physical stress, and psychological stress also appear to play a role in rupture of atherosclerotic plaques. Plaques that are less than 70% obstructive appear to be more likely to undergo rupture, perhaps due to their higher lipid content, thinner fibrous cap and more irregular configuration with the presence of distinct shoulders where shear forces concentrate.

RISK FACTORS

Male gender is a strong predictor of CHD. A large cohort found that men had three times the incidence of CHD as women, with mortality five times higher among men. This increased risk in men declined with increased age. Nearly half this risk was attributable to risk factors more common in men, especially increased smoking and lower high-density lipoprotein (HDL) (LaBounty and Eagle 2007).

Other than advanced age, ***smoking*** is the single most important risk factor for coronary artery disease. Cigarette smoking increases the incidence of AMI by three times in men and six times in women. Passive smoking is now recognized as a modifiable risk factor and consistently associated with a 20 to 30 percent increase in risk. Ischemic heart disease causes 35 to 40 percent of all smoking-related deaths, with an additional 8 percent attributable to second-hand smoke exposure (Libby et al., 2007).

Pathophysiologic studies have identified multiple mechanisms through which cigarette smoking may cause CHD. Oxidative stress plays a central role in smoking-mediated dysfunction of nitric oxide biosynthesis in endothelial cells. Cigarette smoking also lowers HDL-C. These effects, along with direct effects of carbon monoxide and nicotine, produce endothelial damage. Smokers have increased vascular reactivity, reduced oxygen-carrying capacity, a lower threshold for myocardial ischemia, and increased risk of coronary spasm. Cigarette smoking is also associated with increased levels of fibrinogen and increased platelet aggregability (Fuster et al., 2008).