RISK FACTORS FOR THROMBOSIS IN CHILDREN WITH CONGENITAL CYANOTIC HEART DISEASE

Thesis

Submitted for Partial Fulfillment of
M.Sc. in **Pediatrics**

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2013

2013

بسم الله الرحمن الرحيم

سُبْحَانَكَ لاَ عِلْمَ لَنَا
إِلاَّ مَا عَلَّمْتَنَا
إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ

سورة البقرة آية
(32)
صدق الله العظيم

Acknowledgement

First and foremost I would like to thank **ALLAH** *Almighty the most graceful for giving me strength to accomplish this work.*

My deepest gratitude and profound appreciation to Professor Dr. Alyaa Amal Kotby, *professor of Pediatrics, faculty of medicine, Ain Shams University for her meticulous observation, her sincere guidance, her support, her patience and endurance despite her multitude of tasks and burden.*

I would like as well to have the opportunity to express my respect and gratitude to Prof. Dr. Nevin Mohamed Mamdouh, *Assistant Professor of Pediatrics, Faculty of Medicine, Ain Shams University for her endless patience, untiring help, fruitful advice and supervision throughout the period of this study.*

I owe a great dept of gratitude to Dr. Deena Samir Mohamed, *Lecturer of Clinical and Chemical Pathology, Faculty of Medicine, Ain Shams University for her invaluable help and expertise supervision in the practical part of the study.*

I take the opportunity to thank all members of the pediatric cardiology unit *in the children's hospital, Ain Shams University under the supervision of* Professor Dr. Alyaa Amal Kotby *for their help and support during the completion of the study.*

Finally I would like to express my deepest and greatest thanks and gratitude to my family *specially my dear* Dad *and my* Fiancee *for their help, support, patience, endurance, understanding and encouragement to accomplish this work.*

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LIST OF ABBREVIATIONS

Abbrev.	Full term
APC	Activated protein C
aPTT	Activated partial thromboplastin time
ARDS	Adult respiratory distress syndrome
ASD	Atrial septal defect
AUC	Area under the ROC curve
AV	Atrio-ventricular
AVSD	Atrioventricular septal defects
cAMP	Cyclic adenosine monophosphate
CCF	Congestive cardiac failure
CCHD	Congenital cyanotic heart disease
CHD	Congenital heart disease
COA	Coarcatation of aorta
CTDs	Cono-truncal diseases
CVA	Cerebrovascular accident
DIC	Disseminated intravascular coagulation
DORV	Double-Outlet Right Ventricle
EDTA	Ethylene diamine tetraacetic acid
EGF	Epidermal growth factor
EPCR	Endothelial protein c receptor
Hb	Haemoglobin
HCT	Haematocrit
ICAM-1	Intercellular adhesion molecule-1
ID	Iron deficiency
IDA	Iron deficiency anaemia
IE	Infective endocarditis
IL-1B	Interleukin-1B
IM	Inflammatory monocytes
IQR	Interquartile Range
JET	Junctional ectopic tachycardia
LA	Left atriam
LDL	Low-density lipoprotein
LV	Left ventricle
LVF	Left ventricular failure
LVOT	Lt ventricular outflow tract
MAPCAs	Multiple aorto pulmonary collateral arteries
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MTHFR	Methylene tetrahydrofolate reductase
PA	Pulmonary atresia
PBF	Pulmonary blood flow
PC	Protein C

LIST OF ABBREVIATIONS (Cont...)

Abbrev.	Full term
PCR	Polymerase chain reactions
PDA	Patent ductus arteriosus
PLT	Platelet
PS	Protein S
PS	Pulmonary stenosis
PT	Prothrombin time
PVR	Pulmonary vascular resistance
RDW	Red cell distribution width
RFLP	Restriction fragment length polymorphism
RV	Rt ventricle
RVOT	Rt ventricular outflow tract
SD	Standard deviation
SNPs	Single-nucleotide polymorphisms
sTfR	Serum transferritin
SVR	Systemic vascular resistance
TA	Tricuspid Atresia
TA	Truncus arteriosus
TACT	Thrombomodulin addition clotting time
TAFI	Thrombin activatable fibrinolysis inhibitor
TAPVC	Total Anomalous Pulmonary Venous Connection
TGA	Transposition of the Great Arteries
TGF	Transforming growth factor
TIBC	Total iron binding capacity
TM	Thrombomodulin
TNF-α	Tumour necrosis factor-α
TOF	Tetralogy of Fallot
UIBC	Unsaturated iron binging capacity
VA	Ventriculo-arterial
VEGF	Vascular endothelial growth factor

INTRODUCTION

Congenital heart defects are the most common of all congenital malformations, with a review of the literature reporting the incidence at 6 to 8 per 1000 live births ***(Sadowski, 2009).***

It has been recognized for decades that patients with cyanotic congenital heart disease (CCHD) have chronic hypoxia that has serious complications including erythrocytosis, hyperviscosity, abnormalities of hemostasis, cerebral abscesses, stroke, and endocarditis. Erythrocytosis is an adaptive response to improve oxygen transport in CCHD. However, at highly increased hematocrit levels patients may experience hyperviscosity symptoms. Iron deficiency in CCHD patients is often overlooked due to elevated hemoglobin concentrations ***(Brauna et al., 2006)***.

Treatment of hyperviscosity secondary to erythrocytosis in cyanotic heart disease is controversial. Data is limited but suggest that phlebotomy has the potential to increase exercise capacity, reduce the symptoms of hyperviscosity, and reduce the potential risk of vasoocclusive disease in selected patients with polycythemia secondary to cyanotic heart disease. Unfortunately, repeated phlebotomy can quickly lead to iron deficiency, resulting in microcytic erythrocytes that induce higher viscosity than normocytic erythrocytes, which may increase the risk for venoocclusive events ***(DeFilippis et al., 2007).***

Patients with CCHD and associated secondary polycythemia are susceptible to develop coagulation abnormalities. Several coagulation defects, including thrombocytopenia, factor deficiencies, fibrinolysis, and disseminated intravascular coagulation (DIC) have been reported in these patients ***(Tempe and Virmani, 2002).***

The overall mechanisms of thromboembolism in CCHD have not been well clarified. Thrombomodulin (TM) is a vascular endothelial cell receptor present in many cells and tissues. Its density is higher in small vessels and capillaries. It is a critical cofactor for thrombin-mediated activation of protein C and reflects the anticoagulant activity of the endothelium ***(Kajimoto et al., 2007).***

Recent evidence suggests that deranged endothelial function, a sequel of chronic cyanosis, could be an important factor in decreased TM concentration and hence the pathogenesis of cyanosis-associated cardiovascular risk ***(Cordina and Celermajer, 2010).***

AIM OF THE WORK

The aim of this study was to evaluate the role of ID as a risk factor for developing thrombosis in children with CCHD and TM as a detector of thrombosis.

CONGENITAL CYANOTIC HEART DISEASES

Definition

Congenital cardiovascular disease is defined as an abnormality in cardiocirculatory structure or function that is present at birth, even if it is discovered much later ***(Brickner et al., 2000)***.

Incidence

It is approximately 4 to 10 live-born infants per 1000 are affected ***(Pierpont et al., 2007).*** The true incidence of congenital cardiovascular malformations is difficult to determine accurately, partly because of difficulties in definition. About 0.8 % of live births are complicated by a cardiovascular malformation. This figure does not take into account what may be the two most common cardiac anomalies: the congenital, functionally normal bicuspid aortic valve and prolapse of the mitral valve ***(Webb et al., 2008)***.

The incidence of moderate and severe forms of congenital heart disease (CHD) is 6 per 1000 livebirths. If bicuspid aortic valves are included, the incidence rises to 19 per 1000 livebirths ***(Hoffman et al., 2002)***.

Specific defects can show a definite gender preponderance: Patent ductus arteriosus (PDA), Ebstein's

anomaly of the tricuspid valve, and atrial septal defect (ASD) are more common in females, whereas aortic valve stenosis, coarctation of the aorta, hypoplastic left heart, pulmonary and tricuspid atresia, and transposition of the great arteries (TGA) are more common in males ***(Webb et al., 2008)***.

Without early medical or surgical treatment, the majority of patients with complex CHD would not survive to adulthood. Surgical and medical advances over the past 60 years have dramatically altered the once bleak prognosis of patients with CHD. In the current era, more than 85 % of patients with CHD survive to reach adulthood and most live productive and functional lives ***(Warnes et al., 2001)***.

Etiology

Traditionally, CHD was regarded as a sporadic occurrence and was rarely thought to have a genetic cause. Medications during pregnancy (e.g anticonvulsants) and folate deficiency have been implicated, but it is now recognized that many cases of non-syndromic CHD have a genetic component. The risk of having a child with CHD increases if the parents themselves have CHD or a previously affected child. Prenatal Echocardiography is advisable in these cases ***(Wessels and Willems, 2010)***.

The etiology of non-syndromic CHD is a multifactorial complex and results from interaction between genetic

susceptibility and environmental stimulus ***(Botto et al., 2005)***. As the mother is the environment of the child in utero, maternal environmental exposures, such as the intake of vitamins, medicines, and smoking, influence the organ development of the unborn child as well ***(Van Driel et al., 2008).*** The impact of folic acid intake on pregnancy outcome is modified by variants in both maternal and fetal genes that code for critical enzymes in the folate and homocysteine pathways ***(Kotby et al., 2012)***.

Studies have found that impaired folate and homocystiene metabolism affects neural crest cells formation and migration leading to defect in trunco-conal septum and malalignment of outflow tract, resulting in (cono-truncal diseases) CTDs ***(Yelbuz et al., 2002)***. Since Methylene tetrahydrofolate reductase (MTHFR) polymer-phism affects folate and homocystiene metabolism, the presence of such polymorphism can result in impaired folate metabolism,and a resultant defect in neural crest cell formation and migration, and subsequent CTD formation ***(Kotby et al., 2012)***.

Maternal rubella, ingestion of thalidomide and isotretinoin early during gestation, and chronic maternal alcohol abuse are environmental insults known to interfere with normal cardiogenesis in humans. Rubella syndrome consists of cataracts; deafness; microcephaly; and, either singly or in combination, PDA, pulmonary valve and/or arterial stenosis, and ASD ***(Webb et al., 2008)***.