Cardiopulmonary and Renal Risk Factors for Pulmonary Hypertension in Sickle Cell Disease

Thesis

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List of Abbreviations

ACS	Acute Chest Syndrome
ADMA	Asymmetric Dimethylarginine
AHRQ	Agency for Healthcare Research and Quality
ANP	Atrial Natriuretic Peptide
AO	Aortic diameter
ATS	American Thoracic Society
AVN	Avascular Necrosis of Hip and Shoulder
CBC	Complete Blood Picture
cGMP	cyclic Gaunisine Monophosphate
COPD	Chronic Obstructive Pulmonary Disease
CRP	C –Reactive Protein
CSF	Cerebrospinal Fluid
CSSCD	Cooperative Study of Sickle Cell Disease
CT	Computed Tomography
CVS	Chorionic villousSampling
DBP	Diastolic Blood pressure
DDAH	Dimethylarginine Dimethylaminohydrolase
EF	Ejection Fraction
EPCs	Endothelial Progenitor Cells
ESRD	End-Stage Renal Disease
ET-١	Endothelin-١
FS	Fraction Shortening
GFR	Glomerular Filtration Rate
GM-CSF	Granulocyte Monocyte Colony Stimulating Factor
GTP	Gaunisine Triphosphate
HCT	Haemopoietic Cell Transplantation
HDAC	Histone Deacetylase
HDL-C	High-Density Lipo-Protein Cholesterol
HIV	Human Immunodefiency Virus
HLA	Human Leucocytic Antigen
HPLC	High Performance Liquid Chromatography
HR	Heart Rate
IPAH	Idiopathic Pulmonary Arterial Hypertension
IVS	Interventricular Septum Diameter
LA	Left atrial diameter
LA/AO	Left Atrial Diameter/Aortic diameter
LDH	Lactate Dehydrogenase
LVEDD	Left Ventricular End –Diastolic Diameter
LVEDV	Left Ventricular End Diastolic Volume
LVESD	Left Ventricular End Systolic Diameter

LVESV	Left Ventricular End Systolic Volume
LVPW	Left Ventricular Posterior Wall
MBP	Mean Blood Pressure
MCV	Mean Corpuscular Volume
MRI	Magnetic Resonance Imaging
NFKB	Nuclear Factor KB
NIH	National Institutes of Health
NSAID	Nonsteroidal Anti-Inflammatory Drug
NT-proBNP	N-Terminal Pro-brain Natriuretic Peptide
NYHA	New York Heart Association
PA	Pulmonary artery
PAH	Pulmonary Arterial Hypertension
PAP	Pulmonary Artery Pressure
PASP	Pulmonary Artery Systolic Pressure
PCV٧	٧-Valent Pneumococcal Conjugate Vaccine
PDE-٥	Phosphodiesterase-٥
PGD	Preimplantation Genetic Diagnosis
PHT	Pulmonary Hypertension
PlGF	Placental Growth factor
PS	Phosphatidylserine
ROS	Reactive Oxygen Species
RV	Right ventricle
RVEF	Right Ventricle Ejection Fraction
RVSP	Right Ventricular Systolic Pressure
SBP	Systolic Blood Pressure
SCD	Sickle Cell Disease
sFLT-١	Soluble Fms-like tyrosine kinase-١
٦-MWD	٦-Minute-walk distance
٦-MWT	٦-Minute-walk test
TIAS	Transient Ischemic Attacks
TRG	Tricuspid Regurgitant Gradient
TRV	Tricuspid Regurgitant Jet Velocity
VCAM	Vascular Endothelial Cell Adhesion Molecule
VEGFR	Vascular Endothelial Growth Factor Receptor
VOC	Vaso-Occlusive crisis
WHO	World Health Organization

List of Figures

List of Tables

CONTENTS

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Introduction

Pulmonary hypertension (PHT) is an ominous complication in patients with sickle cell disease (SCD) with a reported prevalence ranging from ٢٠ to ٤٠ % ***(Ataga et al., ٢٠٠٤; De Castro et al., ٢٠٠٨).***

The pathogenesis of PHT complicating SCD is probably heterogeneous, including hemolysis and its effect on nitric oxide bioavailability, asplenia, thrombosis, chronic lung disease, and iron overload ***(Lee et al., ٢٠٠٧).***

Echocardiographic estimation of pulmonary artery pressure by measuring the tricuspid valve regurgitant jet velocity (TRV) has been validated as a useful screening method for pulmonary hypertension in adult patients with sickle cell disease ***(Gladwin et al., ٢٠٠٤).*** A jet velocity of ٢,٥ m/sec or more, which corresponds to a systolic pulmonary artery pressure of ٣٠ mmHg or more, has been used for research purposes to define elevated pulmonary artery pressure in adults with sickle cell disease ***(Ataga et al., ٢٠٠٤; Castro & Gladwin., ٢٠٠٥).*** Even though this definition includes mild elevations in pulmonary artery pressure, adult sickle cell disease patients with a regurgitant jet velocity of ٢,٥ m/sec or more have an increased risk of mortality ***(De Castro et al., ٢٠٠٨).*** SCD patients with PHT had a ٤٠-month mortality rate of ٤٠٪ compared with <٢% for those without PHT. This increased risk of death occurs despite milder elevations of pulmonary artery pressure, lower pulmonary vascular resistance, and higher cardiac output than are observed in patients with idiopathic or other forms of secondary PHT ***(Machado & Gladwin., ٢٠٠٥).***

Whether PHT is a direct cause of death in SCD or is a manifestation of multi-organ disease from systemic vasculopathy remains uncertain ***(Kato et al., ٢٠٠٧; Klings., ٢٠٠٨).***

In children with SCD, reports indicate that PHT also occurs with a similar prevalence of about ٣٠٪, but the prognostic significance and natural history of PHT in children with SCD are unknown ***(Kato et al., ٢٠٠٧).***

Epidemiologic risk factors suggested to be associated with PHT in patients with SCD include the following: low hemoglobin levels, high reticulocytic count suggestive of more severe hemolytic anemia; high steady-state serum lactate dehydrogenase (LDH) level, largely reflecting intravascular hemolysis ***(Kato et al., ٢٠٠٦)*** high serum creatinine levels, indicative of renal insufficiency; high serum direct bilirubin and alkaline phosphatase levels, suggesting cholestatic hepatic dysfunction and low serum transferrin or high serum ferritin levels, indicative of iron overload ***(Gladwin et al., ٢٠٠٤)*** In addition, the prevalence of an elevated TRV appears to rise with age during adulthood, exceeding ٦٥٪ after ٥٠ years of age ***(Ataga et al., ٢٠٠٤; Gladwin et al., ٢٠٠٤)*** One study had conflicting findings regarding the relationship of high TRV to systolic blood pressure ***(Ataga et al., ٢٠٠٤)*** Another has found an additional correlation of high TRV to proteinuria ***(De Castro et al., ٢٠٠٨).*** Elevated TRV is also associated with abnormal ٦-minute walk test results ***(Minniti et al., ٢٠٠٩)*** High TRV is significantly correlates with inability to walk >٣٠٠ m in ٦ minutes ***(Aliyu Zakari et al., ٢٠٠٨)*** In men, a history of priapism was also an independent factor associated with PHT ***(Gladwin et al., ٢٠٠٤)*** These data suggest that PHT represents a component of the systemic vasculopathy of SCD (characterized by systemic hypertension, renal failure and priapism), that it is linked to hemolytic rate, iron overload and cholestatic hepatic dysfunction ***(Gladwin et al., ٢٠٠٤).***

There are limited data on the specific management of patients with SCD-PHT. Most of the recommendations are based on expert opinion or extrapolated from data derived from other forms of PHT. The general

approach usually includes maximization of SCD-specific therapy (ie, treatment of primary hemoglobinopathy), treatment of associated cardiopulmonary conditions, general supportive measures and specific therapy for pulmonary hypertension ***(Machado& Gladwin., ٢٠٠٥)***

Aim of the work

To determine the prevalence and risk factors of elevated pulmonary artery pressure (clinical and laboratory) in patients with SCD using Doppler echocardiography especially the cardiopulmonary and renal risk factors.

Sickle Cell Disease

Inheritance:

Sickle cell disease (SCD) is an autosomal recessive disorder, characterized by a single base-pair change, thymine for adenine, at the six codon of the β-gene. This change encodes valine instead of glutamine in the sixth position on the β-globin molecule ***(Madigan & Malik., ٢٠٠٦)***.

Upon deoxygenation, under conditions of hypoxia, acidosis, dehydration, hemoglobin S undergoes conformational changes that expose a hydrophobic region surrounding the valine moiety in the beta-subunit. Polymerization with other hemoglobin tetramers occurs with the formation of long polymer chains that ultimately distort the erythrocyte membrane ***(Gladwin & Kato., ٢٠٠٥)***.

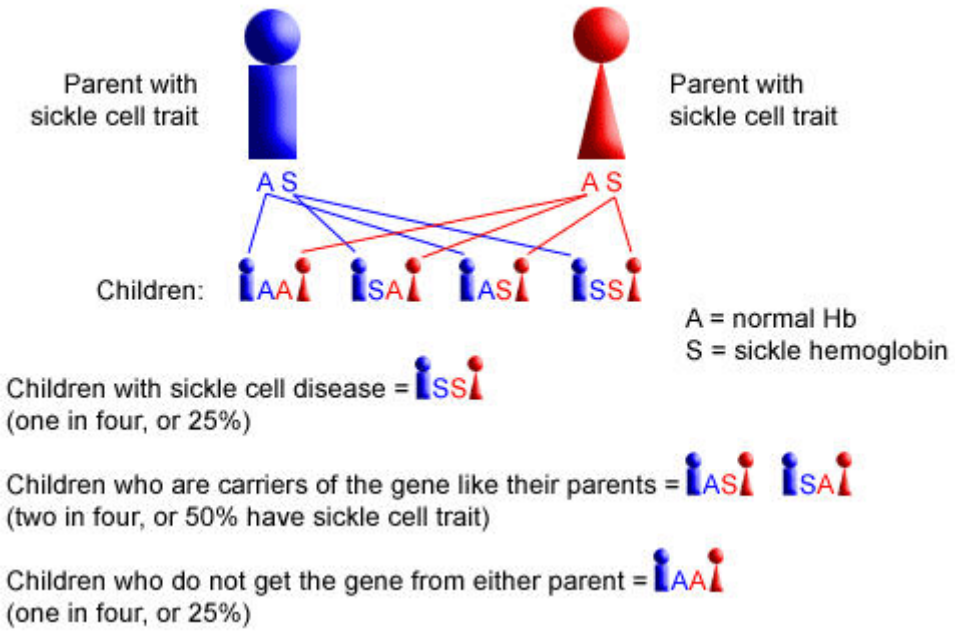

Fig (١): Inheritance of SCD

(Bojanowski et al., ٢٠٠٦)