ADAMTS13 IN β-THALASSEMIC PATIENTS WITH OR WITHOUT HCV INFECTION AND CONTROLS

Thesis

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Lamyaa Zakaria

List of Contents

List of Tables

List of Figures

List of Figures (Cont...)

List of Abbreviations

Abb.	Full term
A	Arginine
ADAMTS13	A-distintegrin metalloprotease thrombospondin 13
Ag	Antigen
AIDS	Acquired immune deficiency syndrome
ALT	Alanin transferase
AST	Aspartate transferase
B-TM	Beta thalassemia major
CBC	Complete blood count
CC 14	Carbon tetrachloride
CD	Cluster of differentiation
CDC	Center of disease control
CT	Computed tomography
DFO	Deferoxamine
DVT	Deep veinous thrombosis
EC	Endothelial cells
ECG	Electrocardiogram
ECM	Extracellular matrix
EGF	Epidermal growth factor
ELISA	Enzyme linked immunosorbent assay
EOT	End of therapy
EPO	Erythropoietin
ESRD	End stage renal disease
G	Glutamine
GTP	Guanosine tri phosphate
HA	Hemolytic anemia
HB	Hemoglobin
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immune deficiency virus

List of Abbreviations (Cont...)

Abb.	Full term
HLA	Human leucocytic antigen
HSC	Hepatic stellate cells
HUS	Hemolytic uremic syndrome
Ig	Immunoglobulin
LC	Liver cirrhosis
LDL	Low density lipoproteins
MCV	Mean corpuscular volume
Mg	Milligram
Ml	Milliliter
MRI	Magnetic resonance imaging
NIBI	Non transferring bound iron
NO	Nitric oxide
PCR	Polymerase chain reaction
PE	Pulmonary embolism
PG	Prostaglandin
PNH	Paroxysmal nocturnal hemoglubinuria
PT	Prothrombin time
PTT	Partial thromboplastin time
RBCs	Red blood cells
RDW	Red cell distribution width
RIBA	Recombinant immune blot assay
RNA	Ribonucleic acid
ROS	Reactive oxygen species
SCD	Sickle cell disease
SEC	Sinusoidal endothelial cells
ss RNA	Single stranded ribonucleic acid
STFR	Soluble transferring receptors
SVR	Sustained virology response
T	Thiamine
TFG	Transforming growth factor

List of Abbreviations (Cont...)

Abb.	Full term
TI	Thalassemia minor
TIBC	Total iron binding capacity
TMA	Thrombtic microangiopathies
TTIs	Transfusion transmitted infections
TTP	Thrombotic thrombocytopenic purpura
TXA2	Thromboxane A2
UL	Unusually large
VWF	Von willibrand factor

Introduction

β-Thalassaemia major is a hereditary hemolytic disorder characterized by a defect in the synthesis of adult haemoglobin beta chains, resulting in ineffective erythropoiesis. Conventional management of β- thalassaemia major requires regular blood transfusion. This leads to excess iron accumulation, initially in the reticuloendothelial system and subsequently in all parenchymal organs, mainly heart, pituitary gland, pancreas and gonads, resulting in serious and sometimes fatal clinical complications ***(Afroditi and Vassilios, 2006).***

Frequent transfusion and subcutaneous desferrioxamine chelation therapy improve the long-term prognosis. But problems related to secondary haemosiderosis are common. These include endocrine complications, liver disease and cardiac failure ***(Roth, 1997).***

Thromboembolic events, such as recurrent and transient ischemic cerebral attacks, strokes, pulmonary embolism, deep venous thrombosis, and portal vein thrombosis, have been observed in thalassemia major patients with a prevalence ranging from 2.5% to 4%. The hypercoagulable state has been attributed to a wide variety of hemostatic alterations including platelet hyperaggregability, protein C and antithrombin deficiency,

increased urinary excretion of thorboxane A2 metabolites, enhanced expression of P-selectin, and procoagulant alterations of red cells. Few studies have evaluated the impact of prothrombotic polymorphisms in thalassemia thrombotic patients ***(Eldor et al., 1999).***

Thromboembolic phenomenona have been described in patients with thalassemia major. In a multicenter, retrospective study investigated the effect of factor V (FV Leiden), prothrombin (FII), methylene tetrahydrofolate reductase (MTHFR) ***(Chiang and Frenette, 2005).***

Patient with thalassemia are at high risk of acquiring a number of viral infections during multiple blood transfusions. Of these infections, hepatitis B and C and human immunodeficiency virus infections are extremely important. Preventing these infections is mandatory for improving survival and quality of life of thalassemic patients. Additionally, iron overload is a major cause of chronic liver disease in patients with β-thalassemia major. Although iron overload is an independent cause of liver dysfunction in thalassemics, the relationship between liver disease and the iron status in anti-HCV (+) patients has been poorly investigated. Hepatitis C virus (HCV) is considered the principal etiologic agent of post-transfusion hepatitis and is the main cause of chronic liver disease in multi-transfused subjects such as patients with β-

thalassemia major. For this reason, HCV infection is found in many thalassemic patients worldwide. HCV isolates also display high levels of sequence heterogeneity, allowing classification into at least 11 types and 90 subtypes. Thalassemic patients may aquire hepatitis C through the administration of HCV-infected blood collected during the donor window period. Moreover, they have a frequent hospitalization, which is an additional risk factor for HCV infection ***(Karimi and Ghavanini, 2001)***.

Aim of the Work

To measure ADAMTS13 level in patients with β-thalassemia major with and without HCV infection and controls of the same age and sex.

Chapter 1

THALASSEMIA

Definition:

The thalassemia syndromes are the most common hereditary chronic hemolytic anemia due to impaired globin chain synthesis ***(Rund and Rachmilewitz, 2005).*** This impairment leads to deficient hemoglobin accumulation, resulting in hypochromic microcytic red cells, ineffective erythropoiesis and hemolytic anemia ***(Takeshita, 2006).*** It is inherited as autosomal recessive disorder ***(Honig, 2000).***

Historical background:

The first definitive descriptions of thalassemia were published independently in the United States and Italy in 1925. In the United States, Cooley, a pediatrician from Detroit, identified a group of children of Mediterranean origin with profound anemia, enlargement of the spleen and peculiar bone changes ***(Weatherall, 2004).*** The unusual name by which the disease is known today was invented by **Whipple** when he was working as a pathologist in Rochester in 1932.Whipple decided on the name "thalassic anemia"-thalassa means sea in Greece and then shortened it to thalassemia. From early as the 1940s, it was clear that the term "thalassemia" is a geographical as well as literary misnomer ***(Weatherall, 2001).***