

Myocardial disease in Egyptian Beta Thalassemia patients

Thesis

Submitted for partial fulfillment of M.Sc degree

in Paediatrics

Presented by

Abd Elhameed Elsayed Abd Elhameed

M.B.B.Ch., Faculty of Medicine Ain Shams University

Under Supervision of

Dr. Azaa Abd El Gawad Tantawy

Professor of Pediatrics

Faculty of Medicine - Ain Shams University

Dr. Neven Mamdoh Habeeb

Professor of Pediatrics

Faculty of Medicine –Ain shams university

Dr. Nayera Hazaa Khalil El Sherif

Assistant professor of pediatrics

Faculty of Medicine –Ain Shams University

Faculty of Medicine

Ain Shams University

2016

أمراض عضلة القلب في مرضى انيميا البحر الابيض المتوسط

رسالة

توطئة للحصول على درجة الماجستير في طب الأطفال

مقدمة من

الطبيب/ عبد الحميد السيد عبد الحميد

بكالوريوس الطب والجراحة - كلية الطب - جامع عين شمس

تحت إشراف

د/ عزة عبد الجواد طنطاوى

أستاذ طب الأطفال

كلية الطب - جامعة عين شمس

د/ نيفين ممدوح حبيب

أستاذ طب الأطفال

كلية الطب - جامعة عين شمس

د / نيرة هزاع خليل الشريف

أستاذ مساعد طب الأطفال - كلية الطب - جامعة عين شمس

كلية الطب

جامعة عين شمس

2016

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

سورة البقرة الآية: ٣٢



*First, I thank **God** for granting me the power to proceed and accomplish this work.*

*I would like to express my deepest gratitude to **Prof. Dr./Azaa Abd El Gawad Tantawy**, Professor of Pediatric , Ain Shams University ,for her valuable supervision and encouragement throughout the accomplishment of this work.*

*I am very grateful to **Prof. Dr./ Neven Mamdoh Habeeb**, Professor of Pediatric , Ain Shams University, for her great help throughout the course of this thesis , She offered me much of her time, effort, scientific support.*

*Words could never express my sincere thanks to **Dr. / Nayera Hazaa Khalil El Sherif**, Assistant Professor of Pediatric , Ain Shams University, for her kind supervision , suggestion of the idea of this work, put the research plane, encouragement and great help throughout the course of this study.*

I am deeply indebted to my family for their generous support and continuous encouragement.

List of Content

Subjects	Page
----------	------

• List of Abbreviation.....	I
• List of Figure	II
• List of Table.....	II
• Abstract.....	VII
• Introduction	1
• Aim of the Study	3
• Review of Literature.....	
• Chapter 1: Cardiac manifestations in beta thalassemia patients.....	4
• Chapter 2: Assessment of cardiac manifestation in Beta thalassemia.....	29
• Patients And Methods	45
• Results	51
• Discussion	96
• Summary	108
• Conclusion	112
• Recommendations.....	113
• References.....	114
• Arabic Summary.....	-

List of Abbreviations

ECG	Electrocardiography
ECHO	Echocardiogram
EF:	Ejection fraction
EPO	<i>Erythropoietin</i>
FS	Fraction Shortening.
GLPS	Global longitudinal peak systolic strain.
GLPS A2C	Global longitudinal peak systolic strain two chambers apical
GLPS A4C	Global longitudinal peak systolic strain four chambers apical
GLPS AVG	Global longitudinal peak systolic strain average
GLPS LAX	Global longitudinal peak systolic strain longitudinal axis
HO-1	Heme-oxygenase1
HRV	Heart rate variability
IL	interleukin
IVSD	Interventricular septum diastole.
LPI	Labile plasma iron
LV	Left ventricular
LVIDd:	Left ventricle internal diameter diastole
LVPWD	Left ventricular posterior wall diastole
MnSOD	manganese-superoxide dismutase
MPs	microparticles
MRI	Magnetic resonance imaging
NO	Nitric oxide
NTBI	Non-transferrin-bound iron
PH	Pulmonary hypertension
ROS	Reactive oxygen species
TDI	Tissue Doppler imaging
TM	Thalassemia major
TNF	Tumor necrosing factor

List of Figures

No.	Figure	Page
Figure (1)	Represents the pathophysiology of iron cardiomyopathy, artificially divided into iron uptake, iron storage, and iron toxicity	10
Figure (2)	<u>Spectrum of illness and the development of heart disease in patients with iron-overload. EC, Excitation-Contraction Coupling; EP, Electrophysiology; HF, Heart Failure; PH, Pulmonary Hypertension. Broken line indicates that some patients may progress rapidly to the dilated cardiomyopathy phase</u>	16
Figure (3)	Mechanism of pulmonary hypertention in beta thalassemia	20
Figure (4)	comparison between patients on mono chelation therapy and those on combined chelation therapy as regard IVSD	66
Figure (5)	comparison between both groups as regard interval between transfusion	73
Figure (6)	comparison between both groups as regard liver enzymes (serum ALT)	75
Figure (7)	comparison between patients with s.ferritin <2500 and patients with s.ferritin >2500 as regard GLPS LAX	78
Figure (8)	comparison between cardiac and non cardiac affected patients as regard total and indirect bilirubin	86
Figure (9)	correlation between mean s.ferritin in the last 2 years and age	88
Figure (10)	correlation between mean s.ferritin in the last 2 years and disease duration	89
Figure (11)	correlation between mean s.ferritin in the last 2 years and interval between transfusion	90
Figure (12)	correlation between mean s.ferritin in the last 2 years and GLPS LAX	92
Figure (13)	correlation between mean s.ferritin in the last 2 years and GLPS A2C	93
Figure (14)	correlation between mean s.ferritin in the last 2 years and GLPS AVG	93
Figure (15)	correlation between cardiac MRI T2 and interval between blood transfusion.	95

List of Tables

No.	Tables	Page
Table (1)	Demographic data of studied patients	51
Table (2)	Laboratory data of studied patients	52
Table (3)	Cardiac evaluation data of studied patients	53
Table (4)	Comparison between males and females beta thalassemia patients as regard M mode echocardiographic data	54
Table (5)	Comparison between males and females beta thalassemia patients as regard speckled echocardiographic data	55
Table (6)	Comparison between males and females beta thalassemia patients as regard percentage of patients with cardiac affection by speakled and those with left ventricular dysfunction by echo M mode.	56
Table (7)	Comparison between males and female beta thalassemia patients with cardiac affection by speckled echocardiography as regard cardiac MRI T2* and liver iron concentration	56
Table (8)	Comparison between splenectomized and nonsplenectomized as regard clinical and transfusion history	57
Table (9)	comparison between splenectomized and non splenectomized patients as regard chelation therapy	58
Table (10)	comparison between splenectomized and non splenectomized patients as regard history of HCV infection	58
Table (11)	Comparison between splenectomized and non splenectomized beta thalassemic patients as regard laboratory data	59
Table (12)	Comparison between splenectomized and non splenectomized beta thalassemia patients as regard M mode echocardiographic data	60
Table (13)	Comparison between splenectomized and non splenectomized beta thalassemia patients as regard speckled echocardiographic data	61

No.	Tables	Page
Table (14)	Comparison between splenectomized and non splenectomized beta thalassemia patients as regard percentage of patients with cardiac affection by speckled and those with left ventricular dysfunction by echocardiography M mode	62
Table (15)	Comparison between splenectomized and non splenectomized beta thalassemia patients as regard cardiac MRIT2* and liver iron concentration (LIC). (done for 10 patients)	63
Table (16)	Comparison between beta thalassemia patients on mono and those on combined chelation therapy as regard laboratory data	64
Table (17)	Comparison between beta thalassemia patients on mono and those on combined chelation therapy as regard M mode echocardiographic data	65
Table (18)	Comparison between beta thalassemia patients on mono and those on combined chelation therapy as regard regard speckled echocardiographic data	67
Table (19)	Comparison between patients on mono and those on combined chelation therapy as regard cardiac affection by speckled and those with left ventricular dysfunction by echocardiography M mode	68
Table (20)	Comparison between cardiac patients by speckled on mono and those on combined chelation therapy as regard cardiac MRI T2* and liver iron concentration (LIC)	69
Table (21)	Comparison between both groups as regard age, sex and family history	70
Table (22)	Comparison between both groups as regard anthropedic measures	71
Table (23)	Comparison between both groups as regard clinical data	72
Table (24)	Comparison between both groups as regard types of Chelation and compliance to it	73
Table (25)	Comparison between both groups as regard laboratory data	74

No.	Tables	Page
Table (26)	Comparison between both groups as regard M mode echocardiographic data	76
Table (27)	Comparison between both groups as regard speckled echocardiographic data	77
Table (28)	comparison between both groups as regard percentage of patients with cardiac affection by speckled and those with left ventricular dysfunction by echocardiography M mode.	78
Table (29)	Comparison between both groups as regard cardiac MRI T2* and hepatic LIC of patients with cardiac affection by speckled echocardiography	79
Table (30)	Demographic ,laboratory ,echocardiographic data of beta thalassemia major patients affected by speckled echocardiography	80
Table (31)	Comparison between beta thalassemia patients with cardiac affection and those without cardiac affection as regard age, sex and family history	81
Table (32)	Comparison between beta thalassemia patients with cardiac affection and those without cardiac affection as regard anthropometric measurements.	82
Table (33)	Comparison between beta thalassemia patients with cardiac affection and those without cardiac affection as regard age of first transfusion history	83
Table (34)	Comparison between beta thalassemia patients with cardiac affection and those without Cardiac affection as regard chelation history and compliance to it	83
Table (35)	Comparison between beta thalassemia patients with cardiac affection and those without cardiac affection as regard percentage of patients with history of HCV infection	84
Table (36)	Comparison between beta thalassemia patients with cardiac affection and those without cardiac affection as regard laboratory data	85
Table (37)	Comparison between beta thalassemia patients with cardiac affection and those without cardiac affection as regard M mode echocardiographic data	87

 List of Tables

No.	Tables	Page
Table (38)	correlation between means.ferritin in the last 2 years and disease duration and age at first blood transfusion	88
Table (39)	correlation between means.ferritin in the last 2 years and interval between transfusion and transfusion requirement	89
Table (40)	correlation between s.ferritin and echocardiographic data	91
Table (41)	correlation between mean s.ferritin and cardiac iron overload by MRIT2* and hepatic iron overload with LIC	94
Table (42)	correlation between cardiac MRI T2* and age at evaluation,age at 1st transfusion and disease duration	94
Table (43)	correlation between cardiac MRI T2 and interval between blood transfusion and transfusion index	95

Abstract

Background: The chronic transfusion, combined with extravascular haemolysis and increased intestinal absorption of iron in BTM patients, leads to significant haemosiderosis of all organs, including the heart. The new parameters of cardiac function, derived from two-dimensional speckle-tracking echocardiography could be useful for an early diagnosis of cardiac involvement in patients with thalassemia major. **Aim:** to detect early myocardial disease in beta thalassemia and to assess the effect of iron load on the myocardium by speckle tracking echocardiography correlating with the efficacy of iron chelation and other risk factors.

Methods: Thirty transfusion dependant β -TM patients were recruited. A detailed medical history (including transfusion, chelation, hepatitis C virus infection history) was gathered from the medical records. Laboratory investigations (CBC, liver function tests, markers of hemolysis), as well as calculation of mean serum ferritin in last 2years were done. Echocardiography (M mode and Speckle Tracking) was done to all patients, while MRI T2* and ECG holter were performed for patients with abnormal speckle echocardiography.

Results: Cardiac affection by speckled echocardiography (elevated longitudinal strain than 11%) was found in 33.3% of BTM patients. There were no significant differences between β TM patients with mean serum ferritin $\geq 2500 \mu\text{g/L}$ and those with serum ferritin $< 2500 \mu\text{g/L}$ as regard M mode echocardiographic parameters. Patients with mean serum ferritin $> 2500 \text{ ng/mL}$ in the last 2 years prior evaluation showed a significantly lower longitudinal strain

(GLPSLAX) ($p=0.043$) which is further proved by the significantly negative correlation with the mean serum ferritin ($p=.002$). There were no significant differences between both splenectomized and non splenectomized patients nor between patients on mono and those on combined chelation therapy as regard echocardiographic data (M mode, speckle). We did not find significant differences between patients with cardiac affection by speckled and those without as regard M mode echocardiographic data. When evaluating the cardiac MRIT2* of the 10 patients with proven myocardial affection by speckled echocardiography, we found that 9 out of 10 patients had low cardiac MRIT2* less than 20 ms and 3 out of 10 patients had low ejection fraction below 60 % .

Conclusion: An abnormal global longitudinal strain despite preserved LV systolic functions; with a significant negative correlation with mean serum ferritin; was observed among BTM patients. Magnetic Resonance Imaging T2* technique is still considered the reference standard in myocardial iron overload, its routine use is limited by its high costs, poor availability, yet speckle tracking echo techniques might be considered as an alternative effective method to detect early myocardial disease before evident systolic dysfunction.

INTRODUCTION

The thalassaemias are common genetic disorders worldwide and they constitute a major problem for patients, health providers and society. Beta thalassemia patients usually require regular blood transfusions to survive, however the chronic transfusion, combined with extravascular haemolysis and increased intestinal absorption of iron, leads to significant haemosiderosis of all organs, including the heart. (*Mavrogeni et al., 2011*).

Cardiac complications such as heart failure and arrhythmias are the major causes of death in Beta Thalassemia patients accounting for up to 67% of death. (*Borgna et al., 2004*). Iron cardiomyopathy is reversible, if chelation starts in time. Once heart failure develops, the prognosis is frequently poor. (*Chouliaras et al ., 2009*)

The incidence of iron overload cardiomyopathy ranges from 11.4 to 15.1% in Beta-Thalassemia major patients (*li et al., 2002*). In the early stage, patients are usually asymptomatic.

Restrictive cardiomyopathy usually occurs before dilated cardiomyopathy, in accordance with diastolic dysfunction which normally happens before systolic dysfunction and overt heart failure. (**De C et al., 2005**).

Speckle-tracking echocardiography is a new non invasive ultrasound imaging technique that allows for an objective and quantitative evaluation of global and regional myocardial function. (**Geyer H et al., 2011**).

The new parameters of cardiac function, derived from two-dimensional speckle-tracking echocardiography could be useful for an early diagnosis of cardiac involvement in patients with thalassemia major (**Ines et al., 2012**).

Currently cardiac MRI (CMR) has been known as a non- invasive technique of choice for monitoring iron overload in the heart (**Mavrogeni et al., 2011**) Cardiac T2* magnetic resonance identifies patients at high risk of heart failure and arrhythmia from myocardial siderosis in thalassemia major and is superior to serum ferritin and liver iron. (**Kirk et al., 2009**)