Correlation between Liver Iron Concentration (LIC) by Liver MRI and Ocular Manifestations of Thalassemia

Thesis

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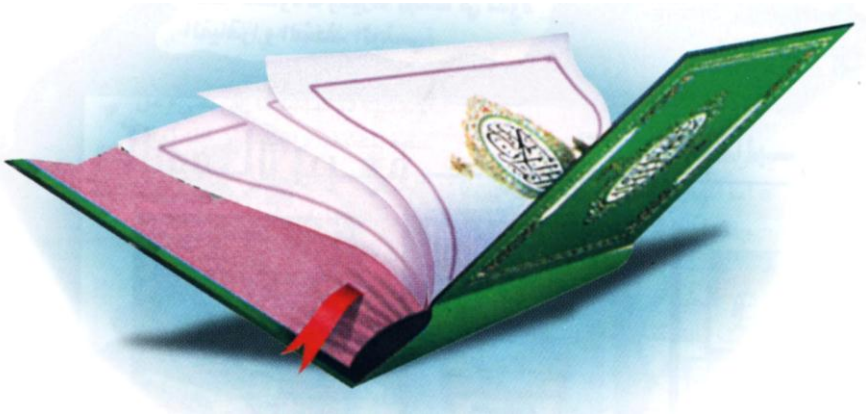
بسم الله الرحمن الرحيم

وَقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ
عَمَلَكُمْ وَرَسُولُهُ وَالْمُؤْمِنُونَ



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Ayman Mostafa Kamel Hussein

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List of Abbreviations

Abb.	Full term
ALT	*Alanine aminotransferase*
AST	*Aspartate aminotransferese*
BIO	*Binocular indirect ophthalmoscope*
CBC	*Complete blood count*
CI	*Confidence interval*
CNS	*Central nervous system*
DFO	*Desferoxamine*
DFP	*Deferiprone*
DFX	*Deferasirox*
DNA	*Deoxyribonucleic acid*
DPD	*Dicholorphyenyldiazoium tetra fluoroborate*
DSB	*Direct serum bilirubin*
ECG	*Electrocardiogram*
EDTA	*Ethylene diamine tetraacetic acid*
ERMA	*Immuno radiometric assay*
G6PD	*Glucose 6 phosphate dehydrogenase*
GDF	*Growth differentiation factor*
GM-CSF	*Granulocyte macrophage colony stimulating factor*
Hb	*Hemoglobin*
HbF	*Fetal Hemoglobin*
HbH	*Hemoglobin H*
HCC	*Hepatocelluar carcinoma*
HCT	*Hematopoietic cell transplantation*
HIF	*Hypoxial inducible transcription factor*
HLA	*Human leucocyte antigen*
HPLC	*High performance liquid chromatography*
HS	*Highly significant*
IFCC	*International federation of clinical chemistry*
IQR	*Interquartile range*
LDH	*Lactate dehydrogenase*
LIC	*Liver iron concentration*

List of Abbreviations

Abb.	Full term
LV	*Left ventricle*
MRI	*Magnetic resonance imaging*
NADH	*Nicotinamide adenine dinucleotide*
NRBCs	*Nucleated red blood cells*
NS	*Non significant*
NTDT	*Non transfusion dependent thalassemia*
OD	*Oculus dexter*
OS	*Oculs sinister*
OTC	*Over the counter*
PRBCs	*Packed red blood cells*
RBC	*Red blood cells*
RIA	*Radioimmuno assay*
RPE	*Retinal pigment epithelium*
SCD	*Sickle cell disease*
SD	*Standard deviation*
SIR	*Signal intensity ratio*
SPSS	*Stasticial package for social sciences*
TDT	*Transfusion dependent thalassemia*
TI	*Thalassemia intermedia*
TIF	*Thalassemia international federation*
TLC	*Total leucocytic count*
TM	*Thalassemia major*
TSAT	*Transferrin saturation*
TSB	*Total serum bilirubin*
VA	*Visual acuity*
VTE	*Venous thromboembolism*
WBC	*White blood cells*

Abstract

Background: Thalassemia is a genetic blood disorder caused by a mutation in the gene encoding for the beta chains. In non-transfusion-dependent-thalassemia, Ocular involvement is not uncommon and may have significant implications.

Aim of the study: We aimed to establish a relation between LIC and ocular manifestations of thalassemia.

Methods: A total of 60 thalassemic patients were subjected to full history (i.e. age, disease duration, chelator type and dosage, frequency of PRBCs transfusion). Clinical examination was performed with emphasis on abdominal examination and ophthalmological examination (including visual acuity testing, fundus and slit lamp examination). Laboratory investigations included CBC, serum ferritin, ALT, AST, TSB and DSB. Imaging studies included liver MRI (i.e. measuring LIC).

Results: The mean visual acuity of the right eye was 0.84 ± 0.17, while it was 0.81 ± 0.17 in the left eye. Regarding slit lamp examination, there were no abnormal findings. fundus examination declared RPE changes in 16.7% of the patients. Concerning LIC, the mean was 3.41 ± 1.68 with a range of 0.52 – 6.08 mg/g.

Conclusion: There is an established correlation between LIC and ocular manifestations of thalassemia.

INTRODUCTION

Thalassemia is a severe genetic blood disorder caused by a mutation in the globin gene. Abnormal globin chains lead to the excessive destruction of red blood cells. The phenotypes of homozygous or genetic heterozygous compound beta-thalassemias include thalassemia major (TM) and thalassemia intermedia (TI). Individuals with thalassemia major usually come to medical attention within the first two years of life. These patients require lifelong RBC transfusions at regular intervals to survive. Thalassemia intermedia includes patients with milder symptoms, who present at an older age and do not require regular transfusions. More than 42,000 newborns are affected by Beta-thalassemia every year worldwide. Without blood transfusions, Beta-thalassemia major (TM) causes death amongst infected children before the age of 3 years old. Although transfusions can prevent death and decrease mortality, iron accumulated from transfused red blood cells can lead to organ failure. Iron chelation treatment, to reduce iron store in the body and improve the long-term survival rate of patients with TM, is considered a mandatory adjuvant therapy (Galanello et al., 2010).

As a group, the thalassemias are the most common single gene disorder in the world. High prevalence occurs in developing regions as well as in large multiethnic Western cities due to an expanding immigrant population. The

inheritance of β-thalassemias is recessive. The mutations in the β-globin gene and consequent defective β-chain production leads to a devastating cascade: imbalance in α/β- globin chain synthesis, ineffective erythropoiesis, reduced red blood cell survival and subsequent anemia. Although the disease is confirmed genetically, the phenotype of β-thalassemia is determined based on clinical observation (Weatherall et al., 2010).

Therapeutic measures resulted in a progressive improvement in life expectancy in both developed and developing countries. Increased awareness, better education and optimal health care provision efforts, a large body of evidence attained by clinical trials and observational studies conducted in the last 3 decades, allowed for remarkable advances in diagnostic and therapeutic options. Milestones in this effort include the introduction of guidelines for safe processing of blood products, noninvasive techniques for the assessment of iron overload in target organs, oral iron chelators, and prevention/management schemes for specific complications (Rachmilewitz et al., 2011).

Thalassemia is a multidimensional medical, social, and psychological problem. The course of thalassemia patients depends on the availability of adequate blood transfusion and other therapeutic modalities. The closer and more systematic follow-up of thalassemia patients, along with the significant improvement of available treatments, prolonged life expectancy

lead to the gradual broadening of the clinical spectrum of beta thalassemia with new, previously unknown manifestations (Aessopos et al., 2002).

The purpose of the present review is to identify the whole spectrum of ocular complications of thalassemia presented in the literature and provide an extensive review on both functional and structural abnormalities related to chelation therapy. We also underline the need for updated guidelines for screening and follow up of thalassemia patients and the proper utilization of multimodal imaging techniques.

AIM OF THE WORK

1- Quantitative assessment of liver iron concentration (LIC) by liver MRI in thalassemic patients.

2- Ophalmological examination for those patients including visual acuity assessment, slit lamp examination and detailed fundus examination.

3- Clinical correlation between LIC and ocular manifestations in those patients by establishing a database including thalassemic patients in the pediatric hematology clinic in Ain Shams university.

Chapter (1)

THALASSEMIA

The thalassemias are a group of disorders in which the normal ratio of alpha globin to beta globin production is disrupted due to a disease-causing variant in one or more of the globin genes. This abnormal alpha- to beta-chain ratio causes the unpaired chains to precipitate and causes destruction of red blood cell precursors in the bone marrow (ineffective erythropoiesis) and circulation (hemolysis). As a result, affected individuals have variable degrees of anemia and extramedullary hematopoiesis, which in turn can cause bone changes, impaired growth, and iron overload (Martin et al., 2013).

EPIDEMIOLOGY — Thalassemia is the most common hemoglobinopathy, with the highest prevalence in historically malaria-endemic areas, including sub-Saharan Africa, the Mediterranean, the Asian-Indian subcontinent, and Southeast Asia. It has been estimated that 5 percent of the world's population has at least one thalassemia variant allele, with as many as 900,000 individuals with clinically significant disease expected during the early 21st century, the majority in Southern China, India, and Southeast Asia (Weatherall et al., 2012).

●**Alpha thalassemia** – Alpha thalassemia is highly prevalent in Southern China, Malaysia, and Thailand. Mild

forms are also commonly encountered in individuals of African origin. As noted above, individuals with Asian ancestry may carry the alpha thalassemia-1 trait (i.e., two alpha gene deletions in cis; aa/--); thus, these individuals are at greater risk of hydrops fetalis. Individuals of African ancestry typically carry the alpha thalassemia-2 trait (i.e., a-/a-) and thus are unlikely to develop hydrops fetalis (Fucharoen et al., 2009).

Beta thalassemia – Beta thalassemia is highly prevalent in Africa. The estimated rate of heterozygosity in the population is approximately 13 % in Africa, 4% in Asia, and 2% in the United States (Vichinsky et al., 2005).

Beta thalassemia creates a social and financial burden for the patients' family and the Egyptian government. The high frequency of beta-thalassemia carriers with increasing rate of newly born cases is a pressing reason for the importance to develop prevention program for beta-thalassemia in Egypt (El-Beshlawy et al., 2009).

Immigration has contributed to greater ethnic diversity of affected individuals and increased prevalence of thalassemia in other countries (Vichinsky et al., 2005).

PATHOPHYSIOLOGY — The major hemoglobin in children and adults is hemoglobin A (adult hemoglobin, HbA), a heterotetramer consisting of one pair of alpha globin chains and one pair of beta globin chains. These chains are derived