Magnetic Resonance spectroscopy in patients with Thalassemia Major

Thesis

Submitted for Partial Fulfillment of Master Degree in Pediatrics

By

Soha Ahmed Hussien Ahmed
M.B.,B.ch., (2007)

Supervisors

Dr. Rasha Hussien Aly Hussien
Asistent Professor of Pediatrics
Faculty of Medicine, Ain Shams University

Dr. Khaled A. Ahmed
Asistent Professor of Diagnostic Radiology
Faculty of Medicine, Ain Shams University

Dr. Rania Hamed Shatla
Asistent Professor of Pediatrics
Faculty of Medicine, Ain Shams University

Faculty of Medicine, Ain Shams University
2014

Acknowledgment

First and foremost, I feel always deeply indebted to Allah, the Most Gracious and the Most Merciful.

I would like to express my deepest gratitude and cardinal appreciation to Prof. Rasha Hussien Ali Hussien, Professor of Pediatrics, who kindly supervised and motivated the performance of this work, for her kind guidance and constant encouragement throughout this work.

I am greatly honored to express my sincere appreciation to Prof. Khaled A. Ahmed, Professor of Diagnostic Radiology, for his continuous support, help and generous advice throughout this work.

I am deeply thankful to Dr. Rania Hamed Shatla, Lecturer of Pediatrics for her great help, outstanding support, active participation and guidance.

Finally, I want to dedicate this work to all the members of my family because of their patience and support.

Soha Ahmed Hussien Ahmed

List of Contents

Title Page No.

List of Tables

Table No.	Title	Page No.

List of Tables (Cont...)

List of Figures

List of Figures (Cont...)

List of Abbreviations

Abb.	Meaning
Ala	Alanine
ALS	amyotrophic lateral sclerosis
BMI	Body mass index
BVRT	Benton Visual Retention Test
Cho	Choline
CNS	Central nervus system
Cr	Creatine
CVA	Cerebrovascular accident
DFO	Desferoxamine
DFP	Deferiprone
DFX	Deferasirox
DWMI	Deep white matter ischemia
Fe	Iron
GABA	Gamma-aminobutyric acid
Gln	Glutamine
Glu	Glutamate
Glx	Glutamate-Glutamine
GMDs	Glucose metabolic disorders
GVHD	Graft versus host disease
Hb	Hemoglobin
Hb F	Fetal hemoglobin
HbA1	Adult hemoglobin1
HbA2	Adult hemoglobin2
HLA	Human leukocyte antigen
H-MRS	Proton MRS
HSCT	Hematopoietic stem cell transplantation
IQ	Intelligence quotient
Lac	Lactate
LIC	Liver iron content
Lip	Lipids
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MS	Multiple sclerosis

List of Abbreviations

Abb.	Meaning
Myo	Myoinositol
NAA	N-acetylaspartate
NAA/Cho	N-acetylaspartate to Choline ratio
NAA/Cr	N-acetylaspartate to Creatine ratio
NAAG	*N* acetyl aspartyl glutamate
NMR	Nuclear Magnetic Resonance
PIH	Pyridoxal isonicotinoyl hydraxone
ppm	Parts per million
RBCs	Red blood cells
RDW	Red cell distribution width
SCD	Sickle cell disease
TE	Time to echo
UCB	Umbilical cord blood
VTEs	Venous thromboembolic events
WCST	Wisconsin Card Sorting Test
WISCIV	Wechsler Intelligence Scale for Children Forth edition
B-TI	Beta thallassemia intermediata
B-TM	Beta thallassemia major

INTRODUCTION

Beta—Thalassemia is prevalent in Mediterranean countries. The Middle East, Central Asia, India, Southern China, and the Far East as well as countries along the total annual incidence of symptomatic individuals is estimated at 1 in 100,000 throughout the world and 1 in 10,000 people in European Union ***(Galanello & Origa ., 2010).***

In Egypt, beta thalassemia is the most common type with a carrier rate varying from 5.3 % - 9 % and a gene frequency of 0.03. So, it was estimated that 1,000 1 /1.5 million per year live births will suffer from thalassemia disease in Egypt (total life births 1,936,205 in 2006 ***(El-Beshilawy & Youssry ., 2009).***

The life expectancy of children with B- TM is increased with transfusion, chelating therapy and bone marrow transplantation. In these patients, complications are generally associated with iron deposition resulting from frequent blood transfusions, hemolysis, and increased intestinal iron absorption, and thus pose a risk for parenchymal organ injuries ***(Duman et al., 2010)***.

Iron deposition mainly affects the liver, heart, pancreas, gonads, parathyroid and thyroid glands, bones, lungs, peripheral and central nervous system (CNS). CNS complications generally present as cognitive dysfunction, which usually results from iron deposition and neurotoxicity of deferoxamine (DFO), which is

commonly used as a chelating agent. Furthermore, hypoxia and thromboemboli may casuse CNS complications and cognitive dysfunction ***(Duman et al., 2010).***

The side effects due to the disease itself or its treatment, being unable to attend school, frequent hospitalizations, and the physical & social restrictions as a consequence of chronic disease and its treatment also lead to cognitive dysfunction ***(Duman et al., 2010).***

Children with untreated Thalassmia major have been reported to experience transient ischemic attacks, silent infarctions that result in brain injury, but often with subtle or undetectable clinical symptoms, and in rare cases not involving chronic transfusion therapy, stroke. A second risk factor, only recently recognized as significant for children with sickle cell disease, is the long-term effect of chronic anemia and associated hypoxia. The third risk factor relates directly to consequences of the treatment that has changed the natural course of this disease ***(Armstrong et al., 2005)***.

In thalassemic patients thrombo-embolic events has been described.

One of the affected organs is the brain where symptomatic and asymptomatic damage has been reported. Recent studies describe cases who preonted with the signs of cerebrovascular accident (CVA), some of them are isehemic

and others with hemorrhage or stroke. They not received regular blood transfusions ***(Khanlarli et al., 1985)***.

Magnetic resonance spectroscopy (MRS) offers a unique, noninvasive approach to assess pediatric neurological abnormalities at microscopic levels by quantifying cellular metabolites. The most widely available MRS method, proton spectroscopy, is approved for general use and can be ordered by clinicians for pediatric neuron imaging studies if indicated ***(Panigraphy et al., 2010).***

MRS can detect changes in intracellular cerebral metabolites. For example MRS can detect decrease in N-acetyl-aspartate containing compounds in chronic hypoxia.Also decrease of choline level as hypoxia decreased choline phosphorylation, choline kinase activity so decrease choline containing compounds Also MRS can detect increase in lactate, glutamate & alanine levels when there is insufficient oxygen at the cellular level ***(Bonavita & Disalle., 1999).***

Detection of NAA containing compounds by MRS in asymptomatic brain damage is indicated specially in group A patients with highly risk to develop thromboembolic events ***(Khanlari et al., 1985).*** As NAA is a marker of neuro/axonal integrity. NAA concentration in white matter is related to the structural and functional integrity of axonal fibers ***(Aydin et al., 2012)***.

Aim of the Work

The aim of this study is uncovering the relation between neurocognitive impairment, serum fetritin and different iron chelators with cerebral intracellular metabolites by doing MRS to B-TM patients.

Chapter (1)

THALASSEMIA

Thalassemia is an inherited autosomal recessive blood disease that originated in the Mediterranean region.In thalassemia the genetic defect, which could be either mutation or deletion, results in reduced rate of synthesis of one of the globin chains causing the formation of abnormal hemoglobin molecule***(Gulbis et al., 2009).***

Prevalence and Geographical Distribution:

It has been estimated that about 1.5% of the global population (80 to 90 million people) are carriers of beta-thalassemia, with about 60,000 symptomatic individuals born annually, the great majority in the developing world ***(Galanello and Origa, 2010).***

In Egypt, it is particularly common in populations of indigenous ethnic minorities of Upper Egypt and also peoples of the Nile Delta, Red Sea Hill Region and especially amongest the Siwan ***(El-Beshlawy et al., 2007).***

Classification of β- thalassemia:

Beta-thalassemia is a genetically inherited hemoglobin disorder caused by impaired synthesis of the β-globin chain, which results in chronic hemolytic anemia. Currently, intensive blood transfusions and iron chelation therapy have improved

the life expectancy and reduced the incidence and severity of cardiac dysfunction and heart failure considerably ***(Mokhtar et al., 2005)***.

1- **β-thalassemia minor:** Heterozygous β- thalassemia is associated with no clinical abnormalities and may be mistaken for iron deficiency anemia***(Honig, 2004)***.

2- **β-thalassemia intermedia (βTI):** About 10% of heterozygous β-thalassemia have a syndrome of intermediate hemolytic severity. Those patients usually have onset of anemia after 2 years of age and they do not require regular blood transfusion ***(Yaish, 2007)***.

3- **β-thalassemia major (βTM):** Homozygous β-thalassemia in which there isdefective formation of β chain ***(Honig, 2004)***.

There are 2 types:

a- β^0 thalassemia: Complete absence of β chain.

b- β^+ thalassemia: β chain synthesis is reduced**.**

4- **Other β-thalassemia syndromes:** Sickle cellβ-thalassemia (Hb-S-β-thalassemia), hemoglobin C- β-thalassemia (Hb-C-β-thalassemia) and hemoglobin D- β – thalassemia (Hb-D-β-thalassemia).

(Yaish, 2007)