MRI Evaluation of hepatic iron overload in chronically transfused β-Thalassemic Children

Thesis

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Samar Sherif Ali Emam

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List of Abbreviations

Abb.	Full term

CT ..... Computed Tomography
Epo ..... Erythropoietin
Fpn1 ..... Ferroportin-1
Ft ..... Ferritin
g/dL ..... Gram per decilitre
GRE ..... Gradient Echo
HAMP ..... Hepcidin antimicrobial peptide
Hb ..... Hemoglobin
HbA ..... Adult hemoglobin A
HbA2 ..... Adult hemoglobin A2
HbF ..... Fetal hemoglobin
HCC ..... Hepatocellular carcinoma
HCV ..... Hepatitis C virus
HS ..... Highly significant
HU ..... Hounsfield unit
Hz ..... Hertz
IQR ..... Interquartile range
IVC ..... inferior vena cava
LIC ..... liver iron concentration
mg ..... Milligram
MRI ..... Magnetic Resonance imaging
ms ..... Millisecond
ng/ml ..... Nanograms per millilitre
NS ..... Non significant
NTBI ..... Non-transferrin bound iron
Pg ..... Picogram

List of Abbreviations Cont...

Abb.	Full term
RBC	Red blood cells
RF	Radiofrequency
RNA	Ribonucleic acid
ROI	Region of interest
ROS	Reactive oxygen species
SD	Standard deviation
SE	Spin Echo
SF	Serum ferritin
SI	Signal intensity
SIR	Signal intensity ratio
SNR	Signal to noise ratio
SQUID	Superconducting quantum interference device
T	Tesla
TBI	Total body iron
TDT	Transfusion dependent thalassemia
TE	Echo time
Tf	Transferrin
TM	Thalassemia major
TR	Time to repeat (Repetition Time)
US	Ultrasound
α	Alpha
β	Beta
γ	Gamma
δ	Delta

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INTRODUCTION

β-Thalassemia major is a hereditary hemolytic anemia characterized by ineffective erythropoiesis and hemolysis. Thalassemia is a major health problem in Egypt since it is estimated that out of 1.5 million live births, 1000 children with thalassemia are born annually. ***(Youssef et al., 2012)***

The treatment of choice for thalassemia patients is blood transfusions. Although it is a life-saving measure, repeated transfusions result in iron deposition within the tissues. This iron overload is exaggerated by intestinal iron absorption stimulated by tissue hypoxia, apoptosis of defective erythroid precursors generated by ineffective erythropoiesis, and hemolysis of native and transfused red blood cells. After repeated transfusions without the use of appropriate chelation therapies, the resulting accumulation of iron may cause endocrine and cardiac dysfunction, hepatic effects, and finally, patient death, which commonly occurs in the second decade of life. ***(Claude & Scott, 2010)***

Liver is the primary site for iron storage in patients with hemochromatosis or transfusion-dependent anemia; therefore, liver iron concentration (LIC) accurately reflects total body iron stores ***(Tziomalos & Perifanis, 2010).***

Ferritin is a metalloprotein that is found in cells. It stores and releases iron in a controlled manner. In normal individuals,

a small amount appears in the circulation and in general reflects the total body iron. It is an acute phase reactant, and the serum levels may be disproportionately greater than the degree of iron loading in infections, inflammatory states, liver dysfunction and malignancies. ***(Azarkeivan et al., 2013)***

Liver core biopsy has a high sampling variability, which limits its utility for quantitative assessment of diffuse liver disease because regional heterogeneity may occur ***(Ratziu et al., 2005).*** Furthermore, liver iron overload cannot be quantified reliably by using US or CT, although severe iron overload can be detected by using CT. For these reasons, noninvasive imaging techniques that allow visualization of the entire liver are desirable for measurement of liver iron. ***(Sirlin & Reeder, 2010)***

MRI is a key tool in the current management of patients with thalassemia. Given its capability of assessing iron overload in different organs noninvasively and without contrast, it has significant advantages over other metrics, including serum ferritin and liver biopsy. LIC can be measured either with relaxometry methods T2*/T2 or signal intensity ratio techniques. ***(Fernandes, 2018)***

MRI machines can generate images at various observation or “echo” times to vary the contrast among different organs. All organs darken with increasing echo time, but those containing iron darken more rapidly. This is due to

the fact that, the magnetic field in a clinical scanner is extremely homogenous, but iron within the tissues creates local magnetic field disturbances that cause the images to darken faster. T2* represents the echo time necessary for a tissue to become twice as dark. Alternatively, image darkening can be expressed by R2*, its rate of darkening. Some investigators prefer to report R2* values rather than T2* values, because R2* is directly proportional to iron concentration. R2* values are simply 1000/T2* and vice versa, making it easily to convert one representation to another. ***(Saggar & Sobti, 2013)***

Aim of the Work

The aim of this study is to assess the role of MRI in the evaluation of hepatic iron overload in multi transfused β-Thalassemic children and to correlate the results with serum ferritin levels.

Chapter 1

LIVER ANATOMY

General Anatomy

The liver is the largest organ, accounting for approximately 2% to 3% of average body weight. Located in the right upper quadrant of the abdominal cavity beneath the right hemidiaphragm. It is protected by the rib cage and maintains its position through peritoneal reflections, referred to as ligamentous attachments. ***(Abdel-Misih and Bloomston, 2010)***

Lobar anatomy

Anatomically the liver is divided into a large right and a small left lobe. These are divided anteriorly by the attachment for the falciform ligament, and on the visceral surface by the grooves for the ligamenta teres and venosum. Two further lobes are described: the caudate lobe posteriorly between the inferior vena cava (IVC) and the fissure for the ligamentum venosum, and the quadrate lobe anteroinferiorly between the gallbladder bed and the fissure for the ligamentum teres. These lobes are part of the conventional right lobe. This division of the lobes bears no relationship to the functional structure of the liver. ***(Ryan et al., 2004)***

Functionally the liver is comprised of two independent right and left lobes, defined by the arterial distribution. Each is supplied by the right and left portal veins and the right or left

hepatic arteries, and each drained by the right or left hepatic duct. The plane of division between these lobes is called the principal plane. There is no external marking of this plane on the anterosuperior surface, but it lies parallel to and about 4 cm to the right of the attachment of the falciform ligament. On the visceral surface the principal plane is defined by the IVC superiorly and the gallbladder bed inferiorly. ***(Ryan et al., 2004)***

In current terminology, the left lobe includes the caudate lobe (which lies between the IVC and the fissure for the ligamentum venosum) and most of the quadrate lobe (which lies between the gallbladder bed and the fissure for the ligamentum teres) ***(Ryan et al., 2004).***

Further subdivision into segments is based on branches of the right and left hepatic arteries. Segments are numbered in the Couinaud system in a clockwise direction starting at the caudate lobe (fig. 1). The caudate lobe is segment I. Segments II and III are the furthest left, divided by the left hepatic vein from segment IV. The left portal vein separates segment II above from segment III below. Segment IV lies between the left hepatic vein and the middle hepatic vein. It is divided into segment IVa above and IVb below by the left portal vein. The right lobe has four segments, divided by the right hepatic vein into anteromedial and posterolateral divisions and by the plane of the right branch of the portal vein into superior and inferior sections. These four segments are numbered in a clockwise fashion from anterior inferomedial: V, VI, VII and VIII. ***(Ryan et al., 2004)***