Early Markers of Renal Affection In Patients with β Thalassemia Major

Thesis submitted in partial fulfillment of the Master Degree
in Paediatrics

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دلالات الكشف المبكر لتأثر الكُلى فى المرضى المصابين بأنيميا البحر الأبيض المتوسط

رســـــالة

توطئة للحصول على درجة الماجستير **فى الأطفال**

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Summary

Beta thalassemia is the commonest type of thalassemia and usually produce severe anemia in their homozygous and compound heterozygous form. The use of regular and frequent blood transfusion in thalassemia has improved life span and quality of life of the patients, but it lead to chronic iron overload.

Severely affected patients are treated by blood transfusion every 3-4 weeks, which results in iron overload in various tissue including the liver heart and endocrine tissue. The kidneys are another site of iron accumulation in thalassemia. Unlike in the other organs, it is unclear whether kidney affection results solely from intravascular hemolysis, chronic transfusion or as a complication of iron chelation therapy.

Beta2-Microglobulin (beta2MG), an interesting and underutilized metabolite, can be used in assessing renal function, particularly in patients suspected of having renal tubulointerstitial disease.

The assay of urinary N-acetyl-beta-D-glucosaminidase (NAG) provides an early indication of tubular dysfunction resulting from renal disease or nephrotoxic damage. False positives are rare and its activity remains high during active disease or a sustained toxic insult but falls to normal levels on

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Mohamed Mustafa Ahmed

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List of Abbreviations

ALT	:	Alanine transferase
AST	:	Aspartate transferase
BM	:	Bone marrow
BMI	:	Body mass index
BUN	:	Blood urea nitrogen
C HS4	:	Chicken hypersensitive site-4 chicken insulator element
Creat	:	Creatinine.
CT	:	Computerized tomography.
DFO	:	Desferrioxamine.
DFT	:	Desferrithiocin.
DM	:	Diabetes mellitus.
ELISA	:	Enzyme liked immunosorbent assay
FS	:	Frame-shifts.
GFR	:	Glomerular filtration rate.
HBED	:	Hydroxybenzyl-ethylenediamine-diaceticacid.
HbF	:	Fetal hemoglobin.
HBV	:	Hepatitis B virus.
HC V	:	Hepatitis C virus .
HCT	:	Haematocrit.
HGB	:	Hemoglobin.
Ht	:	Height.
K	:	Potassium..
LCR	:	Locus control region

List of Abbreviations (Cont.)

LDL	:	Low density lipoprotein
LV	:	Lentiviral
LV	:	Lentiviral
MRI	:	Magnetic resonance image
Na	:	Sodium
NAG	:	N-acetyl beta-D-glucosaminidase
NS	:	Nonsense
PIH	:	Pyridoxal isonicotinovl hydrazone
PRBC	:	Packed red blood cells
RBCs	:	Red blood cells
RIA	:	Radio immune assay
S.TFR	:	Serum Transferrin Receptor
SIN	:	Self-inactivating
SPSS	:	Statistical program for social science
TLC	:	Total leucocytic count
Wt	:	Weight
β	:	Beta
β2MG	:	Beta2 Microglubulin

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Introduction

Beta thalassemia is the commonest type of thalassemia and usually produce severe anemia in their homozygous and compound heterozygous form. The use of regular and frequent blood transfusion in thalassemia has improved life span and quality of life of the patients, but it lead to chronic iron overload ***(Chern et al., 2001).***

Severely affected patients are treated by blood transfusion every 3-4 weeks, which results in iron overload in various tissue including the liver heart and endocrine tissue. The kidneys are another site of iron accumulation in thalassemia. Unlike in the other organs, it is unclear whether kidney affection results solely from intravascular hemolysis, chronic transfusion or as a complication of iron chelation therapy (***Traez et al., 2007***).

Beta 2-Microglobulin (beta 2M), an interesting and underutilized metabolite, can be used in assessing renal function, particularly in patients suspected of having renal tubulointerstitial disease (***Bethea and Forman, 1990).***

The assay of urinary N-acetyl-beta-D-glucosaminidase (NAG) provides an early indication of tubular dysfunction resulting from renal disease or nephrotoxic damage. False positive are rare and its activity remains high during active disease or a sustained toxic insult but falls to normal levels on recovery or removal of the toxin. Urinary NAG activity can be used in conjunction with other tests to assess disease activity and prognosis ***(Price, 1992***).

Aim of the Work

Our study designed to evaluate the prevalence of renal tubular dysfunction among patients with transfusion dependent β-thalassemia major- in the period from January 2009 till June 2011 recruited from the Hematology and Oncology clinic, children's hospital, Ain Shams University.

Thalassemia Syndrome

Definition:

Thalassemia is one of the most common single gene disorders and is widely distributed in the Mediterranean region (***Barragan et al., 2006***). Thalassemia syndromes are a heterogeneous group of inherited anemia's characterized by defects in the synthesis of one or more of the globin chain subunits of the hemoglobin tetramer (***Forget, 2000***).

The thalassemia syndromes are the most common hereditary chronic hemolytic anemia due to impaired globin chain synthesis (***Cighetti, 2002).***

The clinical syndromes associated with thalassemia arise from the combined consequences of inadequate hemoglobin accumulation and unbalanced accumulation of globin subunits. The former causes hypochromia and microcytosis, the latter leads to ineffective erythropoiesis and hemolytic anemia ***(Schwartz et al., 1995).***

Types:

The severity of the imbalance of globin chain generates the different thalassemia phenotypes ***(Scott et al., 1993).***

This disease represents the homozygous state of a partially autosomal dominant gene for which the heterozygous state is associated with much milder hematological changes. The severe homozygous condition is known as thalassemia major, where the heterozygous states were designated according to their severity thalassemia minor or minim. Later, the term thalassemia intermedia was used to describe disorders that are milder than the minor form, but more severe than the traits (***Weatherall, 1995)***.

Thalassemia minor is an asymptomatic disorder associated with prominent abnormalities of erythrocyte morphology but with little or no anemia ***(Lukens, 1993).***

Prevalence and Geographic Distribution:

Thalassemia is considered the most common genetic disorder worldwide, about 3% of the world's population (150 million people) carry β-thalassemia genes and in Southeast Asia 5-10% of the population carry genes for a-thalassemia (***Honig, 2004***).

According to ethnic group, α-thalassemia trait is more prevalent in South East Asia, affect 2.7% of American black newborn and is less common in the Mediterranean region.

β-thalassemia >5% in certain area of Italy, Greece, Sardinia, India and 8% in American black ***(Williams, 2001).***

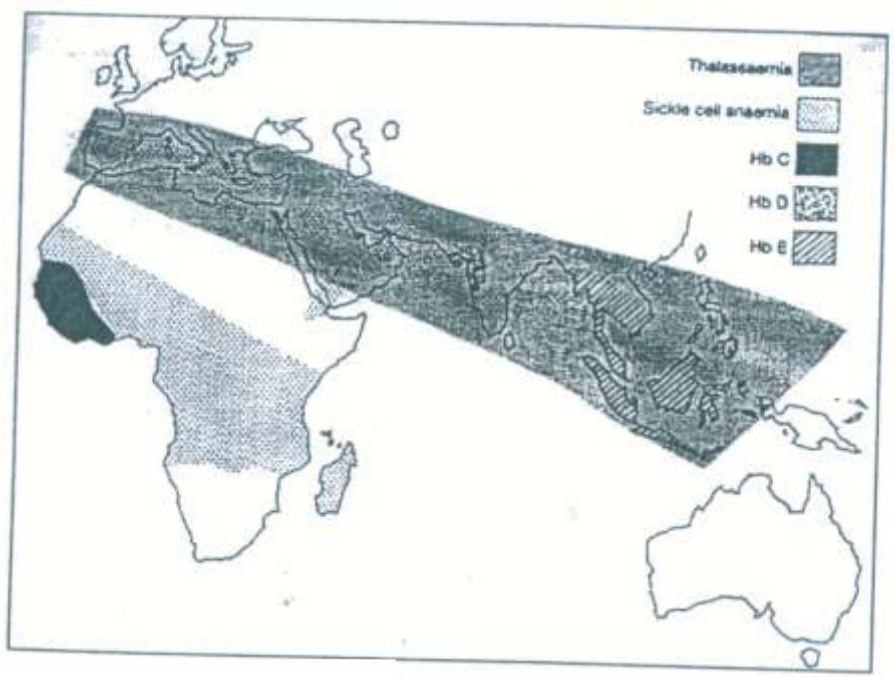

Fig. (1): The geographical distribution of the thalassemias and the more common, inherited structural hemoglobin abnormalities ***(Hoffbrand et al., 2001).***