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Study of Renal Glomerular Dysfunction in Beta Thalassemia Patients in Egypt

Thesis
Study Submitted for
Partial fulfillment of M.Sc. in General pediatrics

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Abstract

Background and objective:

In β-thalassemia, profound anemia and severe hemosiderosis cause functional and physiological abnormalities in various organ systems. In recent years, there have been few published studies mainly in adult demonstrating renal involvement in β-thalassemia. This case control study was aimed to investigate renal involvement in pediatric patients with transfusion dependant beta-thalassemia major, using both conventional and early markers of golmerular dysfunction, and to correlate findings to oxidative stress and iron chelation therapy.

Methods:

Sixty Beta-thalassemia patients (aged 4-18) and 20 healthy controls (aged 4-11) were enrolled in this study. Based age of presentation and frequency of blood transfusion patients were divided into two groups: group (A) 43β-thalassemia major and group (B) 17 β-thalassemia intermedia. We measured level of creatinine, BUN, A/C, GFR using Schwartez formula and creatinine clearance and also serum Cystatin C was measured by immunosorbent assay (ELISA).

Results:

In Beta-thalassemia patients with and without chelation therapy glomerular dysfunction (13.3% had GFR<89 ml/min/1.73m^2,47% had A/C >0.2 mg/dl and 40% had Cystatin C >1257 ng/ml) were reported. The only significant positive correlation was between A/C and serum ferritin in age group >6years .no correlation of Cystatin C with age, duration of the disease serum ferritin and A/C.

Conclusion:

Our data confirm presence of glomerular dysfunction in Beta-thalassemia pediatric patients which could be attributed to iron induced oxidative stress or toxicity of chelation therapy.

Key words:

Renal- glomerular- dysfunction- Beta-thalassemia- Egypt- Cystatin C- Albumin/creatinine (A/C) - GFR- BUN- chelation- pediatric- patients.

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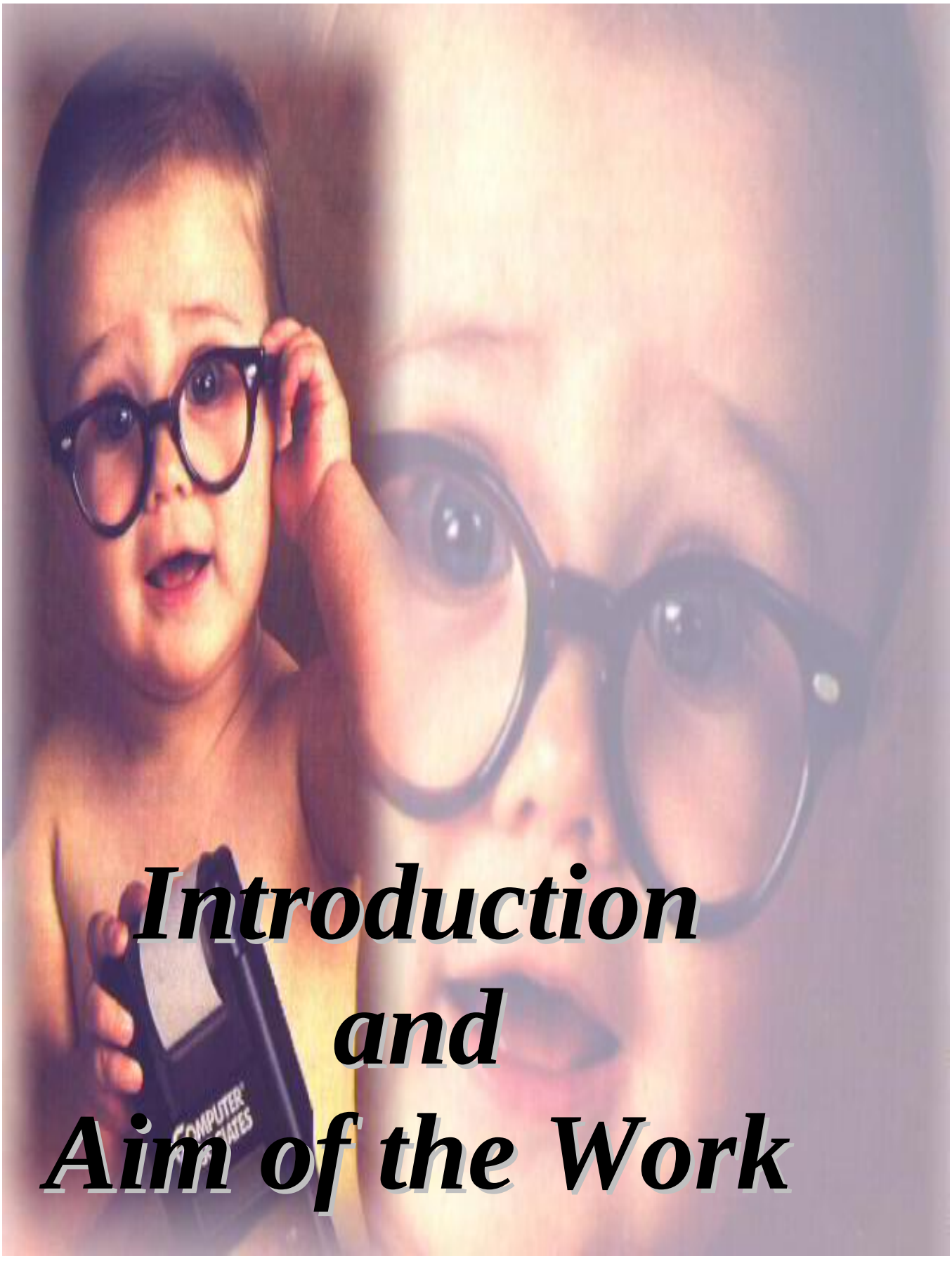

Introduction and Aim of the Work

Introduction

Beta thalassemia major caused by inheritance of 2β globin gene deletion leads to lack adequate production of the β globins .In general, they present between 8 and 10 months of life when fetal hemoglobin production decreases and adult hemoglobin production ensues, the impaired β globin production leads to an excess of α globins which form unstable tetramers and leads to congenital hemolytic anemia ***(olivieri, 1999).***

In beta thalassemia, regular red cell transfusions relieve the severe anemia, reduce the compensatory bone marrow expansion, and prolong survival ***(Cohen and Kwiatkowski, 2004).***

Patients with thalassemia major who may become transfusion-dependent and receive excess iron with each transfusion (that the body has no means to excrete), iron gradually accumulates in various tissues, causing morbidity and mortality. Each unit of transfused blood has approximately 250 mg of iron ***(Mir and Logue, 2008).***

Iron -induced cardiac disease remains the main cause of death in patients with thalassemia major ***(Borgna-Pignatti et al., 1998).***

Abnormalities of renal functions have also been reported by various studies. ***Walton et al., 1997*** reported that patients with thalassemia major have higher levels of proteinuria and urinary loss of low molecular weight proteins ***(Walton et al., 1998).***

Various glomerular pathologies have been sporadically reported and it is still unknown whether those abnormalities are genuinely associated with the thalassemic syndromes. One study of ten patients with Cooley's anemia suggested some abnormalities associated with renal medulla. Renal tubular acidosis has also been reported in patients with thalassemia ***(Aldudak et al., 1999).***

Aim of the work

This work aims at studying renal glomerular dysfunction of Beta thalassemia patient in Egypt with special attention to biochemical markers useful for early detection of such dysfunction and its correlation to different disease parameter.


Review
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Chapter (I)

Thalassemia

Thalassemia

Thalassemia is a group of inherited disease of blood. About 100,000 Babies worldwide are born with severe forms of thalassemia each year. The Disease occurs most frequently in middle East, Southern Asian, Italian, Greek, and African ancestry ***(Eldor and Rachmilewitz, 2002).***

1-Historical background:

In 1925, Thomas Cooley and Pearl lee described a form of severe anemia, occurring in children of Italian origin and associated with splenomegaly, severe growth retardation, and characteristic bone changes **(*Cooley and Lee, 1925).*** Over the next decade, a milder form was described by several Italian investigator ***(Rietti, 1925)*** because all early cases were reported in children of Mediterranean origin, this disease was termed later thalassemia, from the Greek word "Thalassemia" meaning "sea" and "emia", which means "related to blood" **(*Cooley et al., 1927 and Whipple et al., 1932).***Over the next 20 years, it became apparent that Cooley and Lee had described the homozygous or compound heterozygous state for a recessive mendelian disorder not confined to the Mediterranean people only, but occurring widely throughout tropical Countries. In the past 20 years, the two important forms of this disorder α and β thalassemia, resulting from the defective synthesis of the alpha and beta globin chains of hemoglobin, respectively, have become recognized as most common monogenic disease in human **(*Weatherall and Clegg, 1996; Olivier, 1999).***

2-Distribution and population at risk:

Thalassemia is considered the most common genetic disorder Worldwide, about 3% of the world population carry beta thalassemia gene **(*Lukens, 1993; Bernard, 2000***). Estimates of gene frequencies range from 3 to 10% in some areas as Southeast Asia **(*Honig, 2004*).**

Thalassemia is the most common in the Mediterranean, equatorial or near equatorial region of Africa and Asia. The thalassemia belt extends along the shores of the Mediterranean and throughout the Arabian peninsula, turkey, Iran, India and Southeastern Asia, especially Thailand, Cambodia and Southern China. The frequencies of the gene in these regions range from 2.5 to 15% ***(Hoffman, 1995).***

Worldwide, about 60000 children with thalassemia major are born annually and about 150 million people carry thalassemia genes ***(Cao, 2002).***

In Egypt, homozygous Beta thalassemia was first described by Diwani, ***(1944*)** who described three children with cooley's anemia. Two of these children were genuine Egyptians while the third was Greek ancestry**.** Recently the hematology Clinic at Cairo University Children's Hospital reported a carrier rate varying between 6 and 10%. Thalassemia represents 20% of all cases visiting the clinic and 80% of the chronic hemolytic anemia patients. Also it was estimated that 1,000 children affected with thalassemia are expected out of 1.5 million live births per year **(*El-Beshlawy, 2003*)**

3-Human Hemoglobin:

1-Structure and function of hemoglobin:

Oxygen is transported from the lungs to the tissues by highly specialized protein molecules called hemoglobin, which is located in the red cells of the blood **(*Honig, 2004*)**. Each red blood cell contains 300 million molecules of these proteins, totaling about 30 picograms in weight per cell. Each hemoglobin molecule is formed by two pairs of identical sub-units called the globin chains. Humans have the genes to construct six types of globins, but do not use all six at once. Different globins are produced depending on the stage of development ***(Maton et al., 2003).***