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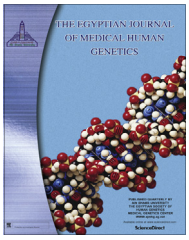

ORIGINAL ARTICLE

Subclinical renal abnormalities in young thalassemia major and intermedia patients and its relation to chelation therapy

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KEYWORDS

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Abstract *Background:* Limited data are available about renal involvement in thalassemia patients. Renal dysfunction in these patients seems to be multifactorial attributed mainly to long standing anemia, chronic hypoxia, iron overload and toxicity of iron chelators.

Objective: To assess the frequency of subclinical glomerular and tubular dysfunctions in children and adolescents with β-thalassemia major and intermedia, and to correlate these findings with the degree of iron overload and type of chelation therapy.

Methods: The study included 40 thalassemia major and 20 thalassemia intermedia pediatric patients recruited from the Pediatric hematology clinic, Ain Shams University. Serum sodium, potassium, phosphorous and creatinine, and urinary sodium, potassium, phosphorous, protein/creatinine ratio and urinary β2 microglobulin were measured. Fractional excretion of sodium and potassium was calculated.

Results: The mean level of serum creatinine in all patients was within the normal range and comparable in both TM and TI groups (0.17 ± 0.06 and 0.18 ± 0.07 mg/dl, respectively, $P > 0.05$). The mean eGFR was higher than normal range in both TM and TI groups (552.65 ± 231.73 and 472.15 ± 272.99 ml/min, respectively). Mean level of urinary β2 microglobulin was within the normal range (0.13 ± 0.05 and 0.10 ± 0.03 μg/ml) in TM and TI patients, however, it was significantly higher in TM patients ($P = 0.009$). Urinary β2 microglobulin was positively correlated to

Abbreviations: A/C, albumin/creatinine ratio; β2MG, urinary β2 microglobulin; CBC, complete blood count; FENa, fractional excretion of sodium; FEK, fractional excretion of potassium; Hb, hemoglobin; HPLC, high-performance liquid chromatography; NAG, *N*-acetyl-β-d-glucosaminidase; TM, thalassemia major; TI, thalassemia intermedia; U pr/Cr ratio, urinary protein/creatinine ratio

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both transfusion index and serum ferritin level ($P < 0.05$). Tubular reabsorption of phosphorus (TRP) was significantly higher among TM patients ($P = 0.037$). The mean height and height percentile were lower in the poorly chelated group (serum ferritin $\geqslant$2500 ng/ml) than the well chelated group. In addition, the mean serum sodium and urinary protein/creatinine ratio were significantly higher in the poorly chelated group ($P < 0.05$).

Conclusion: Subclinical renal affection can start earlier in TM patients compared to TI. Poor chelation is associated with early signs of renal affection. Periodic renal assessment of those patients is mandatory as they may be affected by hidden renal dysfunction.

1. Introduction

β-Thalassemias are a group of hereditary blood disorders characterized by anomalies in the synthesis of the β chains of hemoglobin (Hb) resulting in variable phenotypes ranging from severe anemia to clinically asymptomatic individuals [1]. β-Thalassemia intermedia (β-TI) encompasses a wide clinical spectrum of the β-thalassemia (β-thal) phenotype. Some β-TI patients are asymptomatic until adult life, whereas others are symptomatic from as young as 2 years of age [2]. The severity of β-TI depends on the degree of imbalance between α and non-α chains as well as other genetic and environmental factors that modify the natural history of the disease [3]. β-Thalassemia major (β-TM) is an inherited Hb disorder characterized by chronic anemia and iron overload due to transfusion therapy and gastrointestinal absorption. Iron overload causes most of the associated mortality and morbidity [1,4]. A number of clinical complications are commonly associated with β-TI, affecting the lives of patients. Prevention of these complications is ideal since they may be difficult to manage [5,6]. The cost of providing lifelong medical care to patients with thalassemia according to the standards adopted in the developed countries is extremely high. The burden of thalassemia imposed on the health systems of developing countries is unbearable [7].

With increased duration of survival of children with β-thalassemia major, the effects of iron overload in the liver, pancreas, and heart become more severe, however renal involvement has received little attention [8]. Renal dysfunction may occur in β-thalassemia major patients showing no clinical symptoms and before the manifestations of any other complications [9]. Renal dysfunction in these patients is not known well and seems to be multifactorial; attributed mainly to long-standing anemia, chronic hypoxia, iron overload and toxicity of iron chelators [10].

1.1. Objective

This study aimed to investigate the frequency of subclinical glomerular and tubular dysfunctions in children and adolescents with β-thalassemia major and β-thalassemia intermedia, and to correlate these findings with the degree of iron overload and type of chelation therapy.

2. Patients and methods

This cross sectional study included 60 patients recruited from the regular attendants of the Pediatric Hematology Clinic, Pediatric Hospital, Ain Shams University. Patients were divided into two groups; Group 1 consisted of 40 patients with β thalassemia major (18 males and 22 females) with age ranging from 2.5 to 18 years and with a mean age of 10.78 ± 4.03 years, and Group 2 consisted of 20 patients with β thalassemia intermedia (11 males and 9 females) with age ranging from 2.5 to 15 years and with a mean age of 8.78 ± 3.45 years. Group 1 patients were further subdivided into 2 groups according to the serum ferritin level: Well chelated group (with serum ferritin $<$2500 ng/ml) that included 30 patients, 14 males and 16 females, with age ranging from 3 to 18 years and mean age of 11.35 ± 4.25 years. Poorly chelated group (with serum ferritin $\geqslant$2500 ng/ml) that included 10 patients, 4 males and 6 females with age ranging from 2.5 to 12 years and a mean age of 9.1 ± 2.8 years. The procedures applied in this study were approved by the parents of children as well as approved by the Ethics Committee of Human Experimentation of Ain Shams University, and are in accordance with the Helsinki Declaration of 1975.

2.1. Diagnostic criteria of thalassemia patients

Diagnosis of each type of thalassemia was based on age at presentation, markers of chronic hemolysis as well as qualitative and quantitative analysis of Hb. The studied β-TI patients had the following criteria at the time of initial diagnosis; age at presentation was more than 2 years, mean Hb level of 8–10 g/dl, HbF $<$ 50% and HbA2 $>$ 4%. The criteria of β-TM patients at the time of initial diagnosis were: age at presentation was less than 2 years, mean Hb level of 6–7 g/dl, HbF $>$ 50% and HbA2 $<$ 4% [11]. Exclusion criteria for patients under this study included other hemoglobinopathies (thalassemia minor or sickle-thalassemia), any associated hemolytic disorder (e.g., glucose 6-phosphate dehydrogenase deficiency), those with urinary tract infection at time of sampling and patients with serum creatinine above the upper normal limit for age.

The main indications for splenectomy in the studied thalassemia patients were hypersplenism, splenic pain, leucopenia and thrombocytopenia, growth retardation, severe exercise intolerance, increased transfusion demand or symptomatic splenomegaly [12]. For transfusion status, transfusion therapy was initiated in β-TI patients mainly for failure to thrive in childhood, bone deformities, progressive splenic enlargement, persistent worsening anemia, or development of complications during the course of the disease. β-Thalassemia major patients were transfused on regular interval transfusion protocols based on Hb level (once every 2–5 weeks for a pre transfusion Hb of $<$7.0 g/dl). Iron chelation therapy was administered for at