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Research article

Renal iron deposition by magnetic resonance imaging in pediatric β-thalassemia major patients: Relation to renal biomarkers, total body iron and chelation therapy

Mohsen Saleh ElAlfy[a], Nayera Hazaa Khalil Elsherif[a,*], Fatma Soliman Elsayed Ebeid[a], Eman Abdel Rahman Ismail[b], Khaled Aboulfotouh Ahmed[c], Yasser Wagih Darwish[b], Ahmed Samir Ibrahim[c], Islam Reda Farag Elghamry[a], Nermeen Adel Shokrey[a], Dunia Naser Alajeil[a]

[a] Pediatrics Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt
[b] Clinical Pathology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt
[c] Radiology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt

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ABSTRACT

Background: The reciprocal of multiecho gradient-echo (ME–GRE) T2* magnetic resonance imaging (MRI) R2*, rises linearly with tissue iron concentration in both heart and liver. Little is known about renal iron deposition in β-thalassemia major (β-TM).

Aim: To assess renal iron overload by MRI and its relation to total body iron and renal function among 50 pediatric patients with β-TM.

Methods: Serum ferritin, serum cystatin C, urinary albumin creatinine ratio (UACR), and urinary β2-microglobulin (β2 M) were measured with calculation of β2 M/albumin ratio. Quantification of liver, heart and kidney iron overload was done by MRI.

Results: Serum cystatin C, UACR and urinary β2 microglobulin as well as urinary β2m/albumin were significantly higher in β-TM patients than the control group. No significant difference was found as regards renal R2* between Patients with mean serum ferritin above 2500 μg/L and those with lower serum cutoff. Renal R2* was higher in patients with poor compliance to chelation therapy and positively correlated to indirect bilirubin, LDH, cystatin C and LIC but inversely correlated to cardiac T2*.

Conclusion: kidney iron deposition impairs renal glomerular and tubular functions in pediatric patients with β-TM and is related to hemolysis, total body iron overload and poor compliance to chelation.

1. Introduction

Iron overload is a common complication of thalassemia syndromes which could lead to organ damage and increased morbidity and mortality [1]. High levels of local iron in the kidney can cause kidney injury that can eventually progress to end stage renal disease. Renal damage may develop through tubule-interstitial and/or glomerular injuries [2]. The success that has been made in the care of patients with thalassemia has led to the emergence of unrecognized complications including several renal abnormalities [3]. Iron chelation therapy can ameliorate these complications but close monitoring of tissue iron is important to track iron accumulation and iron removal therapies [4].

Multiecho gradient-echo (ME–GRE) T2* magnetic resonance imaging (MRI) is an established technique for noninvasive and reproducible assessment of iron overload in the heart and liver [5]. Renal ME-GRE T2* also appears to be a feasible and reproducible method that has been used for evaluating renal iron overload in thalassemia patients [6]. The reciprocal of T2* known as R2* has been shown to rise linearly with chronically determined tissue iron concentration in both heart and liver [7]. The pathophysiologic significance of kidney R2* is unclear. It may have a value as a long-term measure of hemolysis and could be a surrogate for renal iron accumulation in chronically transfused patients [4,6].

Few studies directly investigated kidney iron deposition in β-thalassemia major (β-TM) [4,5]. Therefore, we assessed renal iron overload by MRI and its relation to liver iron concentration (LIC), cardiac

* Corresponding author at: Abbaseya square, Eldemerdash Hospital, Cairo, Egypt.
E-mail address: nayeraelsherif@med.asu.edu.eg (N.H. Khalil Elsherif).

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T2* and biochemical markers of glomerular and tubular function as well as the relation to type of chelating agent and compliance to chelation therapy among pediatric patients with β-TM.

2. Materials and methods

This cross-sectional study included 50 patients with transfusion-dependent β-TM (≤18 years); 25 males and 25 females who were randomly recruited from the regular attendants of the Pediatric Hematology Clinic, Ain Shams University. They were compared to 25 age- and sex-matched healthy individuals enrolled as controls. The control group was proven to be healthy after full clinical examination and laboratory investigations. The mean age of patients was 12.8 ± 3.2 years, while the control group had a mean age of 11.6 ± 3.3 years. An ascent form was signed by patients and controls and informed consent was signed by the guardian of each patient or control before participation. The procedures applied in this study were approved by the Ethical Committee of Human Experimentation of Ain Shams University.

All patients were diagnosed with β-TM based on quantitative analysis of hemoglobin using high performance liquid chromatography (HPLC). Exclusion criteria were any evidence of infection, α-thalassemia, sickle β-thalassemia, symptomatic renal or cardiac disease, hypertension according to age, diabetes mellitus, hypothyroidism, rheumatoid arthritis or other autoimmune diseases.

All included patients were subjected to detailed medical history and thorough clinical examination with special emphasis on disease duration, anthropometric measures, blood pressure, evidence of cardiac disease, viral hepatitis, history of splenectomy, transfusion history (calculated as the transfusion index: volume of transfused packed red cells in ml per kg body weight per year; expressed as the mean value in the last two years) and chelation therapy.

Patients with β-TM received either mono or combined chelation therapy. Mono-chelation was in the form of deferoxamine (DFO) infused subcutaneously in a dose that ranged from 30 to 45 mg/kg/d given subcutaneous using the pump over 8–10 h 5 days/week, oral deferiprone (DFP) in a daily dose that ranged from 75 to 100 mg/kg/d, divided over 3 doses or oral deferasirox (DFX) in a dose 20–40 mg/kg/d once daily. Compliance to chelation therapy was assessed by reviewing patient self-report of dose-taking and the appropriate number of doses taken during each day was checked by prescription refills and pill count; a cutoff point below 80% was considered as poor compliance to the regimen [8]. According to literature, serum ferritin cutoff value 2500 μg/L was used to classify patients into 2 groups as it was defined to be the best for prediction of thalassemia complication [9].

2.1. Laboratory analysis

Laboratory investigations included CBC using Sysmex XT-1800i (Sysmex, Kobe, Japan), examination of Leishman-stained smears for differential white blood cell (WBC) count, hemoglobin analysis by HPLC using D-10 (BioRad, Marnes La Coquette, France), liver function tests (serum albumin, total and direct bilirubin, alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), markers of hemolysis (lactate dehydrogenase [LDH] and indirect bilirubin) using Cobas Integra 800 (Roche Diagnostics, Mannheim, Germany). Serum ferritin level was measured on Immulite 1000 analyzer (Siemens Healthcare Diagnostics, Marburg, Germany) at the start of the study with calculation of the mean value of the last year prior to the study in order to know the ferritin trend. Urinary albumin excretion (UAE) was assessed in an early morning fasting urine sample as albumin-to-creatinine ratio by an immuno-turbidimetric method (Cobas C111; Roche Diagnostics, Mannheim, Germany). Patients were classified according to UAE in at least 2 out of 3 consecutive urine samples, 2 months apart into 3 groups; the normoalbuminuria group (UAE < 30 mg/g creatinine), microalbuminuria group (30–299 mg/g creatinine) or the macroalbuminuria group (UAE ≥ 300 mg/g creatinine) [10]. Urinary β2-microglobulin (β2 M) was assessed by enzyme linked immunosorbent assay (ELISA) using DBC Diagnostics Biochem Canada Inc., Ontario, Canada. Urinary β2 M/albumin ratio was calculated. Serum levels of cystatin C were measured by ELISA using kit supplied by SinoGeneclon Co., Ltd (Hangzhou, China).

2.2. Sample collection

Peripheral venous blood samples were collected on potassium-ethylene diamine tetra-acetic acid (K2-EDTA) (1.2 mg/mL) for CBC and hemoglobin analysis. For chemical analysis and enzyme linked immunosorbent assay (ELISA), clotted samples were obtained and serum was separated by centrifugation for 15 min then stored at −80 °C till subsequent use.

2.3. MRI acquisition and image analysis

All patients underwent MRI examination using a 1.5-T scanner (Philips-Intera, Holland) Achieva MR Unit and a 12-element phased array coil. No Gadolinium based contrast agent (GBCA) was used for any of our Patients. Patients were evaluated for liver siderosis using relaxation parameter T2*. LIC measurements were conducted by acquiring eight consequent T2* values and assessing T2* decay. Liver T2* values were converted into LIC values using the calibration curve [11]. LIC of > 7 mg Fe/g dry liver weight was found to be the best threshold for determining the presence of hepatic siderosis [12]

For the measurement of myocardial T2*, a single short 20 s breath-hold axis mid-ventricular slice was acquired at eight simultaneously acquired echo times (TEs 1.4–13.6 ms/echospacing 1.6 ms). The myocardial T2* was calculated using the same method as that in the liver. Cardiac T2* < 10 milliseconds (msec) denotes high risk while 10–20 msec denotes intermediate risk and > 20 msec defines low risk patients [13].

Kidney R2* was measured in five axial slices, covering the pancreatic and renal area; each slice was acquired in a single end-expiratory breath-hold by an ME–GRE T2* sequence. Sequence parameters were: ten echo times (TEs), spaced from 1.2 msec to 13.9 msec. The mean renal T2* value was calculated as the average of T2* values in the two kidneys. To evaluate intra-observer variability, the images were analysed twice by the same radiologist. To evaluate the inter-observer variability, the same images were analysed by two different radiologists blinded to each other's results. Patients were compared to control values corresponded to the standards for age and gender reported elsewhere [4,5,14]. The lower limit of normal for the mean kidney T2* value was 31 msec [5]. The total liver, cardiac and renal MRI scan duration was 15 min. During MRI assessments, all patients were cooperative and tolerated the techniques.

2.4. Statistical analysis

Analysis of data was done using Statistical Program for Social Science version 21 (SPSS Inc., Chicago, IL, USA). Quantitative variables were described in the form of mean and standard deviation or median and interquartile range (IQR; 75th and 25th percentiles). Qualitative variables were described as number and percent. Kolmogrov Smirnov test was used for testing the distribution of normality. In order to compare parametric quantitative variables between two groups, Student *t*-test was applied. For comparison of non-parametric quantitative variables between two groups, Mann-Whitney test was used. Qualitative variables were compared using Chi-square (X^2) test or Fischer's exact test when frequencies were below five. Pearson correlation coefficients were used to assess the association between two normally distributed variables. When a variable was not normally distributed, a Spearman correlation test was performed. Multivariable linear regression analysis was employed to determine the relation