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Growth differentiation factor-15 in children and adolescents with thalassemia intermedia: Relation to subclinical atherosclerosis and pulmonary vasculopathy

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ABSTRACT

Background: Heart disease is the leading cause of mortality and one of the main causes of morbidity in β-thalassemia. Growth differentiation factor-15 (GDF-15), a member of the transforming growth factor-β superfamily, is a marker of ineffective erythropoiesis in several anemias.
Aim: To determine GDF-15 levels in children and adolescents with TI and the relation to hemolysis, iron overload and cardiovascular complications.
Methods: GDF-15 was measured in 35 TI patients without symptoms for heart disease and correlated to echocardiographic parameters and carotid intima media thickness (CIMT).
Results: GDF-15 levels were significantly higher in TI patients compared with controls ($p < 0.001$). Transfusion dependent patients had higher GDF-15 than non-transfusion dependent patients. TI patients with splenectomy, pulmonary hypertension risk, and heart disease had higher GDF-15 levels than those without. GDF-15 was lower among hydroxyurea-treated patients. Multiple linear regression analysis revealed that transfusion index ($p = 0.012$), serum ferritin ($p < 0.001$), tricuspid regurgitant jet velocity ($p < 0.001$), ejection fraction ($p = 0.01$) and CIMT ($p = 0.007$) were independently related to GDF-15. According to ROC curve analysis, the cutoff value of GDF-15 at 1500 pg/mL could differentiate patients with and without heart disease.
Conclusion: GDF-15 would identify TI patients at increased risk of pulmonary and cardiovascular complications as well as subclinical atherosclerosis.

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1. Introduction

Thalassemia intermedia (TI) is a less well-defined clinical entity which encompasses thalassemia patients with a wide spectrum of phenotypes that are more severe than thalassemia minor but milder than thalassemia major (TM) [1]. Patients with TI usually present to medical attention in later childhood or even adulthood. They show mild to moderate anemia and a hemoglobin level ranging between 7 and 10 g/dL, which is sustainable without the need for regular transfusion therapy [2]. Nearly 10% of β-thalassemia patients have β-TI [3].

Heart disease is the leading cause of mortality and one of the main causes of morbidity in β-thalassemia. Two main factors determine cardiac disease in this form. One is the high output state that results from chronic tissue hypoxia and from hypoxia-induced compensatory reactions. The other is the vascular involvement that leads to an increased pulmonary vascular resistance and an increased systemic vascular stiffness. Valvular abnormalities and iron overload also contribute to a less extent. As a result, both right and left ventricles have to maintain a high cardiac output level through a stiff vascular bed. Right heart involvement with age-related pulmonary hypertension followed by congestive heart failure dominates the clinical picture [4]. Iron-mediated endothelial dysfunction may be mediated either directly through the inactivation of endothelium-derive nitric oxide (NO) or indirectly through the promotion of reactive oxygen species formation [5].

Carotid intima-media thickness (CIMT) testing is recognized as a valid method for the noninvasive assessment of atherosclerosis. In addition to its association with known cardiovascular risk factors and both prevalent and incident coronary heart disease, the rate of CIMT progression is directly related to the risk for future cardiovascular events [6].

Growth differentiation factor-15 (GDF-15) is a protein belonging to the transforming growth factor-β superfamily, which includes several proteins involved in tissue homeostasis, differentiation, remodeling and repair [7]. As a pleiotropic cytokine it is involved in the stress response program of different cell types after cellular injury. Under

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normal conditions, GDF-15 is only weakly expressed in most tissues [8]. However GDF-15 is strongly upregulated in disease states such as acute injury, tissue hypoxia, inflammation and oxidative stress [9,10].

GDF-15 was identified as a hepcidin suppression factor that is expressed at high levels in patients with ineffective erythropoiesis [11]. GDF-15 levels were found to be significantly elevated in patients with β-TM [12] and TI [13] as well as sickle cell disease (SCD) [14]. The aim of the study was to determine serum levels of GDF-15 in children and adolescents with TI in relation to patients' characteristics, iron overload, hemolysis and therapy and to assess its value as a potential marker for cardiovascular complications and subclinical atherosclerosis.

2. Materials and methods

This cross sectional study included 35 patients with β-TI (17 males and 18 females) recruited from the regular attendants of the Pediatric Hematology Clinic, Pediatric Hospital, Ain Shams University. Thirty five age- and sex-matched healthy subjects were enrolled as a control group (22 males and 13 females). The median age of TI patients was 10.2 years (range: 3.5–18 years) while that of controls was 9.1 (range: 3–17 years). An informed consent was obtained from 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, and are in accordance with the Helsinki Declaration of 1975.

All patients were diagnosed with TI based on criteria previously described [15,16]. Exclusion criteria were any evidence of active hepatitis [serum transaminases >3 times above upper limit of normal (ULN)] or renal impairment (serum creatinine >3 times ULN), inflammation, diabetes mellitus, 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, evidence of renal, hepatic or cardiac disease and splenectomy status. The main indications for splenectomy were growth retardation or poor health; leukopenia; thrombocytopenia; increased transfusion demand; or symptomatic splenomegaly [3]. For transfusion status, patients were classified as follows: transfusion-dependent (patients on regular-interval transfusion protocols [once every 1–3 months for a pre-transfusion hemoglobin of ≥8 g/dL] initiated 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); transfusion independent (patients who required incidental transfusions for transient severe anemia secondary to infections or surgery). The transfusion received was calculated as the transfusion index: volume of transfused packed red cells in mL per kg body weight per year (expressed as the mean value of the last three years).

Twenty patients received hydroxyurea (Bristol-Myers-Squibb, NY, USA) as an oral daily dose ranging from 15–25 mg/kg/day. Chelation therapy was in the form of deferoxamine (Desferal®, DFO; Novartis Pharma AG, Basel, Switzerland) subcutaneously in a dose ranged from 30–45 mg/kg/day given 5 days/week, or an oral iron chelator (deferiprone, L1) in a dose ranged from 50–100 mg/kg/day divided on three doses for 5 days/week for those with serum ferritin >1000 μg/L.

2.1. Sample collection

Peripheral blood samples were collected on potassium-ethylene diamine tetra-acetic acid (K2-EDTA) (1.2 mg/mL) for complete blood count (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 at 1000 ×g then stored at −20 °C till subsequent use in ELISA.

2.2. Laboratory analysis

Laboratory investigations included CBC using Sysmex XT-1800i (Sysmex, Japan) with assessment of mean pre-transfusion hemoglobin, examination of Leishman-stained smears for differential white blood cell (WBC) count, hemoglobin analysis by high performance liquid chromatography (HPLC) using D-10 (BioRad, Marnes La Coquette, France), liver and kidney function tests, markers of hemolysis (lactate dehydrogenase [LDH] and indirect bilirubin) and high sensitivity C-reactive protein (hs-CRP) as well as serum ferritin on Cobas Integra 800 (Roche Diagnostics, Mannheim, Germany). Patients with any clinical evidence of infection or CRP >10 mg/L were excluded. Serum ferritin level was measured 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. Determination of serum levels of GDF-15 was done by ELISA using Quantikine Human GDF-15 Immunoassay (R&D systems, Minneapolis, Minnesota).

2.3. Echocardiography

All studied patients were clinically asymptomatic for pulmonary hypertension and cardiovascular abnormalities. Screening for pulmonary hypertension was performed by the non-invasive Doppler echocardiography with different modalities using Vivid E9 (GE Healthcare, Norway) to evaluate right and left ventricle function, pulmonary artery pressure and tricuspid regurgitant jet velocity (TRV). A TRV ≥2.5 m/s was used as a proxy for patients at risk for pulmonary hypertension [17,18]. Heart disease was defined by at systolic left ventricle (LV) dysfunction (LV shortening fraction <30% or LV ejection fraction <55%) [19]. The E/A ratio is a marker of the function of the ventricle of the heart; it is determined on echocardiography, an ultrasound-based cardiac imaging modality. Abnormalities in the E/A ratio on Doppler echocardiography suggest that the ventricle, which pumps blood into the circulation, cannot fill with blood properly in the period between contractions. This phenomenon is referred to as diastolic dysfunction and can eventually lead to the symptoms of heart failure [20].

2.4. Measurement of CIMT

All of the carotid scans were done using a carotid Doppler ultrasound scanner (Vivid 7, GE, Horten, Norway) with a 7.5-MHz linear array transducer. The left and right common carotid arteries were imaged in a standardized magnification (2 × 2 cm) with images of the posterior wall of the distal 10 mm of the common carotid artery, just proximal to the carotid bulb. Images were captured when both the anterior and posterior wall margins were clearly seen, to ensure that the images were taken perpendicular to the vessel. A minimum of 4 images of each of the common carotid arteries were taken. All images were taken at end-diastole, incident with the R-wave on a continuously recorded electrocardiogram and then digitally stored for later analysis. The 3 best quality images for each of the carotid arteries were selected and analyzed. Best quality was defined with those images that produced the most number of points for analysis. For each image, the greatest distance between the lumen–intima interface and media adventitia interface (intima media thickness [IMT]) was measured at a minimum of 100 points. The mean and maximum IMT of each image were then averaged to give the final result for each subject [21].

2.5. Statistical analysis

Analysis of data was done using Statistical Program for Social Science version 15 (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. In order to compare parametric quantitative variables between two groups, Student's *t*-test was applied.

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