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Impact of beta thalassemia on maxillary sinuses and sino-nasal passages: A case control study

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ABSTRACT

Objectives: Skeletal changes among beta (β) thalassemia children are well documented, but without available data regarding sino-nasal passages alterations. The authors investigated the maxillary sinuses and sino-nasal passages changes in β-thalassemia children and correlated such changes with the amount of transfused red cells and the erythroid marrow activity.

Methods: Clinical analyses including otorhinolaryngical examination (ORL) were obtained in twenty β-thalassemia children and 20 matched healthy controls. Hemoglobin (Hb), serum ferritin, soluble transferrin receptor (sTfR) levels and bone mineral density of the lumbar spine (BMD ls) were assayed. The two groups were analyzed for the CT image parameters: bone thickness, anterior and posterior choanae diameters, extramedullary hematopoiesis and chronic rhinosinusitis (CRS)

Results: Nasal congestion/obstruction was identified in 14 (70%) children. Eight patients (40%) had criteria of chronic rhinosinusitis. In comparison with the normal controls, the increase in the roof, floor, medial, anterior, lateral and posterior maxillary bony walls thickness was significantly higher (1.26, 2.46, 2.6, 2.9, 3.23 and 5.34-folds, respectively). The mean posterior choanae horizontal, vertical diameters and their surface area were significantly reduced in the patients compared to the controls. The mean anterior maxillary wall bone thickness directly correlated with sTfR ($P = 0.047$) while that of the posterior wall correlated inversely with Hb level ($P = 0.013$). The mean vertical posterior choanae diameter had positive correlation with the amount of transfused red cells ($P = 0.001$) and negative correlation with sTfR ($P = 0.001$). The Hounsfield unit of maxillary sinus wall had direct relation with BMDls ($P = 0.003$)

Conclusions: Thalassemia children are at risk of different folds increase of maxillary sinuses walls thicknesses utmost at posterior and lateral walls. Other sino-nasal morbidities include diminished posterior choanal diameter, nasal obstruction and CRS. Certain morbidities had relations to the erythroid marrow activity and the transfusion adequacy.

1. Introduction

Thalassemias are genetically determined disorders of hemoglobin (Hb) synthesis with decreased production of either alpha (alpha thalassemia) or beta (beta thalassemia) polypeptide chains of hemoglobin [1]. They are the most common monogenetic diseases worldwide [2,3].

Beta (β) thalassemia is particularly prevalent among Mediterranean. This disorder is a major health problem in Egypt with an estimated carrier rate of 9–10.2% [4]. The spectrum of thalassemias is diverse, with one end comprising, thalassemia major (TM) characterized by patients who present in their first year of life with profound anemia and regular transfusion requirements for survival, while on the other end thalassemia minor, which consists of mild even asymptomatic microcytic anemia. In between the thalassemia intermedia exists with non-transfusion dependent phenotype [1].

Thalassemias resulted in 25,000 deaths in 2013 down from 36,000 deaths in 1990. Concern is increasing that thalassemias may become a very serious problem in the next 50 years [5].

Ineffective erythropoiesis (IE), due to excess production of free alpha (α)-globin chains, is the hallmark of β-thalassemia. IE results in profound anemia and triggers a number of compensatory mechanisms responsible for the clinical sequelae associated with

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β-thalassemia such as erythroid marrow expansion, extramedullary hematopoiesis (EMH), splenomegaly, and increased gastrointestinal iron absorption [6]. Depending on the severity of IE, the erythroid marrow can expand resulting in severe skeletal deformities and osteopenia. In addition, both the increase in plasma volume caused by marrow expansion and splenomegaly exacerbate anemia and increase transfusion requirements [7]. Soluble transferrin receptor (sTfR) is a truncated form of tissue receptors [8], whose main source is the erythroid marrow [9]. Anemia associated with expanded but ineffective erythropoiesis involves the presence of large amounts of TfR on erythroid cells and the production of large amounts of soluble receptor in the serum [10]. Previous studies demonstrated that the sTfR concentration was a good indicator for evaluating the erythroid marrow activity in different genotypes of thalassemia [11,12].

The severity of the skeletal responses in β-thalassemia is related to the type of thalassemia, the type of treatment, the amount of red blood cells (RBCs) consumed per year, as well as the side effects of chelation therapy and the bone involved [7]. Characteristically, the maxillary bones and sinuses are one of the earliest well developed bone with a red marrow in its wall which is absent in the ethmoid sinuses. Although, predominantly thalassemia affects the rapidly growing long bones [7], proliferation of marrow and hypertrophy of osseous structures of the maxillary bones in such disease is expected. Such changes can bring about sinonasal predicaments; affecting the external shape of the face, pneumatization of the paranasal sinuses and patency of the osteomeatal complex (OMC) as well as the nasal cavities. All such expected changes with its impact on sino-nasal structure and function were not studied yet. Also Vitamin D deficiency is reported to be high among thalassemic patients in many countries despite the presence of good sunshine and routine prescription of 400–1000 IU vitamin D per day [13]. So the risk of vitamin D deficiency in thalassemia cannot only lead to bone disease but to chronic rhinosinusitis (CRS) as well. As otorhinolaryngology (ORL) surgeons are not attentive with possible sino-nasal alterations in thalassemia patients [14] misinterpretation and complications in diagnosis and treatment can be expected.

Two other factors necessitate conducting the present study: the multiple co-morbidities which impede the managing doctors to search for changes in their sino-nasal passages and the lack of knowledge about the relation between possible sino-nasal airway changes and the known thalassemia disease parameters.

So, the aim of the present study was to evaluate the changes of the maxillary sinuses and sino-nasal passages in thalassemia children and to correlate such changes with the amount of transfused red cells and the erythroid marrow activity.

2. Materials and methods

2.1. Study population

The present prospective controlled study included 20 β-thalassemia children recruited from the Pediatric Hematology Clinic, Menoufia University Hospital, Egypt. Twenty normal age and sex matched healthy children were involved as controls.

The patient group included 15 thalassemia major (TM) and 5 thalassemia intermedia (TI) children. TM children were transfusion dependant on a regular blood transfusion regimen (every 3–4 weeks) since infancy to maintain pre-transfusion Hb above 7 g/dl and post transfusion Hb above 10 g/dl. TI was non-transfusion dependant who had received either only sporadic blood transfusions or on less frequent transfusion (every 2–3 months).

For both patient categories, chelation therapy was usually started when serum ferritin approximated 1000 ng/ml. Chelation was either by subcutaneous deferoxamine infusion in a dose of 30–50 mg/kg/day,5 days/week, oral deferasirox (20–30 mg/kg/day),oral deferiprone (75 mg/kg/day) or combined therapy of both DFO three days/week and daily oral deferasirox.

The controls were healthy children with normal complete blood count (CBC) and Hb electrophoresis and with no family history of any chronic hemolytic anemia or ORL complaint. They had been randomly selected from children presented to CT radiology unite for other non-ORL causes. Complete pediatric and ORL assessment was done for them that revealed no abnormalities.

The study was performed between June 2014 and June 2015. Informed consent was obtained from the legal guardians of the studied children and the ethical committee and Internal Review Board of Menoufia University Faculty of Medicine had approved the study.

2.2. The clinical, laboratory and bone mineral density assessment of the studied groups

Thalassemia children were subjected to detailed history taking and thorough clinical examination. Special emphasis was given for the age of the disease diagnosis, time of the first blood transfusion, frequency of blood transfusion with calculation of RBCs transfusion index (RBCsTI) during the last year, chelation therapy details, and history of splenectomy. Other relevant data were retrieved from patients' files.

All included children were submitted to the followings:

- Complete blood count (CBC) using AC920 Auto-counter after calibration (Pre transfusion samples were considered for the patient group).
- Serum ferritin level was measured by enzyme linked immune sorbent assay (ELISA) (Ramco Laboratories Inc., Stafford, TX, USA). The mean yearly serum ferritin level in the previous year was considered (on the average of 4 determinations) for patients with single estimation for the controls.
- Soluble transferrin receptors (sTfR) estimation with Human sTfR ELISA Kit (BioVendor, Research, and diagnostic products) following the manufacturer's protocol.
- Bone mineral density (BMD) measurement of the lumbar spine (ls) using dual-energy X-ray absorptiometry (DEXA) scan (Norland – XR-46, USA).

2.3. Sino-nasal symptoms, clinical and CT parameters

All included children were subjected to evaluation of the nasal symptoms (rhinorrhea, nasal stuffiness/congestion, nasal itching, and sneezing, facial pain and headache). Symptoms were just asked for but not scored. Mongoloid features was graded into mild, moderate and severe together with complete ORL examination including 0 degree nasal endoscopic examination. According to European position paper on rhinosinusitis and nasal polyps (EPOS 2012) [15], chronic rhinosinusitis (CRS) was identified if 12 weeks or longer of two or more of the following signs and symptoms existed: mucopurulent drainage (anterior, posterior, or both), nasal obstruction (congestion), facial pain-pressure-fullness, or cough. Inflammation is documented by one or more of the following findings: purulent (not clear) mucus or edema in the middle meatus or anterior ethmoid region, polyps in nasal cavity or the middle meatus, and/or radiographic imaging showing inflammation of the paranasal sinuses. CRS CT scan findings was graded using the validated Lund–Mackay score according to EPOS 2012[15].

2.4. CT Nose and paranasal sinuses examination

It was conducted using 16-multidetector CT scanner, Toshiba Alexion (Japan). The examination is performed as a helical scanning