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Original Article

Short-term Assessment of HSCT Effects on the Hypothalamus-Pituitary Axis in Pediatric Thalassemic Patients

Amir Ali Hamidieh, MD[1]; Fariba Mohseni, MD[2]; Maryam Behfar, MD[3]; Zohreh Hamidi, MD, MPH[2]; Kamran Alimoghaddam, MD[3]; Mohamad Pajouhi, MD[2]; Bagher Larijani, MD[2]; Mohammad-Reza Mohajeri-Tehrani, MD[2*]; Ardeshir Ghavamzadeh, MD[3]

[1]Pediatric Stem Cell Transplant Department Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
[2]Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
[3]Hematology-Oncology and Stem Cell Transplantation Research Center of Tehran University of Medical Sciences, Tehran, Iran

Abstract

Background: Beta thalassemia major (BTM) and its treatment by hematopoietic stem cell transplantation (HSCT) may have deleterious effects on the endocrine systems. We assessed endocrine complications of HSCT in pediatric patients for 3 months.

Methods: In 20 (6 female) pediatric major thalassemic patients (mean age of 10.8 ± 3.9 years old), prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), T4, T3, thyroid-stimulating hormone (TSH), IGF-1, testosterone (in males) or estradiol (in females) were measured as a batch at the Endocrinology and Metabolism Research Center (EMRC) of Tehran University of Medical Sciences (TUMS) laboratories before HSCT and 1 and 3 months afterwards. The cosyntropin test for all and the clonidine test for short stature patients was conducted before HSCT.

Results: Before HSCT, delayed puberty and hypogonadotropic hypogonadism was found in 10% and 20% of patients, respectively. GH deficiency, low IGF1 and short stature was found in 25%, 55% and 40% of patients, respectively. Hypocortisolism, hypothyroidism and panhypopituitarism was found in 15%, 10% and 15% of patients, respectively. Prevalence of hypogonadotropic hypogonadism, low IGF1, hypothyroidism and panhypopituitarism was found in 20%, 40%, 10% and 10% of patients after 3 months, respectively (delayed puberty and short stature prevalence do not change after 3 months). HSCT caused lower T3 and estradiol and higher TSH. Corticosteroid users (15) had higher GH and lower T3 and testosterone or estradiol. Ferritin had a significant (negative) correlation with (before) prolactin and a significant correlation with T3 and T4 after HSCT. Age and acute graft-versus-host disease (GVHD) had no significant effect.

Conclusion: Considering the small sample size and short duration of the study, it is difficult to reach any conclusion however it seems HSCT does not appear to have an overall positive or negative effect on prevalence of pituitary- hypothalamus axis disorders in pediatric thalassemic patients in 3 months.

Keywords: Endocrine disorders, HSCT, Hypothalamus, Pituitary, Thalassaemia

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Introduction

Up to now, each year, near 15000 hematopoietic stem cell transplantations (HSCTs) are performed around the world. One-third of these are children and at least 2000 of them are expected to be long-term survivors.[1] With such high number of survivors, systemic determination of risk factors for morbidity in pediatric patients is very important. Of course, some risk factors, like gender,[2] are not modifiable, but more information is equal to better future designs of HSCT processes to avoid sequelae. Since some side effects of HSCT, such as delayed puberty or osteoporosis, may appear some years later,[3,4] the current medical care for survivors depends on such investigation for better care in surveillance, counseling and early intervention. Some side effects of HSCT include renal, cardiovascular, pulmonary, neurocognitive, and endocrine disorders. Endocrine disorders reported as one of the most common consequences.[1] Contact with chemotherapeutic drugs, chronic Graft-versus-host disease (GVHD), and long-term corticosteroids consumption are main causes of endocrine disorders. In hemoglobinopathies, hemochromatosis before stem cell transplantation is also a risk factor.[5]

Busulfan-cyclophosphamide (Bu-Cy), is a common used myeloablative. It is used in both gender and especially in adults and may lead to permanent infertility. Prolonged chronic GVHD also has negative effect on sperm counts[6] and also on bone density.[7]

HSCT endocrine complications are even more important in non-malignant diseases because the immediate survival of patients is not the main goal. Patient quality of life is an important aspect of transplantation. One of these diseases is beta thalassemia major (BTM) or Cooley's anemia.

***Corresponding Author:** Mohammad-Reza Mohajeri-Tehrani, MD; Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran. 5th Floor, Shariati Hospital, North kargar Ave., Tehran 14114, Iran. Fax: +9821-88220052, Tel: +9821-88220037-38, Email: mrmohajeri@tums.ac.ir.

These patients need blood transfusions to live. Iron overload or hemochromatosis, due to hyper-blood transfusion, causes endocrine disorders like reduction of sex steroids, impaired GH secretion, diabetes, hypoparathyroidism, hypothyroidism, and osteoporosis.[8,9] Iron chelating therapy reduces such iron overload, but it has its complications as well. Therefore, use of HSCT as a curative alternative for thalassemia major patients is recommended.

However these curative treatments- theoretically provider for a transfusion-free life for patients- but even HSCT has its own side effects. Some side effects of HSCT occur during the first and the third month after transplantation. After 3 months, we can divide side effects into 3 categories: delayed (3 months–2 years), late (2–10 years), and very late (>10 years) complications.[3]

Because, the first 3 months after transplantation is very critical, and no comprehensive data is available, we planned this study to examine endocrine changes in pediatric major thalassemic patients in a short-term period after HSCT.

Materials and Methods

Study Protocol

Twenty major beta-thalassemia patients, 2–17 years of age, entered this study. Female to male ratio was 6:14. Exclusion criteria included any known preexisting medical condition (other than BTM or subclinical hypothyroidism) and chronic systemic administration of steroids. A medical history was obtained by interview. Study participants underwent hormonal blood evaluation including serum ferritin, IGF1, prolactin, T3, T4 and thyroid-stimulating hormone (TSH), luteinizing hormone (LH) and follicle-stimulating hormone (FSH), testosterone (males), and estradiol (females) measurements. Before HSCT, all patients underwent the cosyntropin test. Patients with <3 height percentile did the clonidine GH stimulation tests. Mean of demographic and anthropometric parameters and medical history are shown in Table 1.

Patient Characteristics at HSCT

This study recruited all β-thalassemia patients being transplanted in the pediatric unit of the Hematology, Oncology and stem cell transplantation Research Center at Shariati hospital (a Tehran University of Medical Sciences hospital). The medical history and details on disease control were obtained from chart reviews. Our center had the policy to transplant all transfusion-dependent BTM patients who had HLA identical related donors regardless of their disease severity. The class 1 and class 2 patients were prepared for transplantation with a combination of busulfan 3.5 mg/kg PO daily in divided doses for 4 days (-8 to -5), cyclophosphamide 50 mg/kg once daily IV for 4 days (-4 to -1) and horse antithymocyte globulin 5 mg/kg daily IV for 2 days (-2 to -1). HSCT conditioning used for class 3 patients included busulphan 3.5 mg/kg kg PO in divided doses daily for 4 days (-8 to -5) and cyclophosphamide 40 mg/kg once daily IV for 4 days (-4 to -1). No one in the study received total body irradiation therapy. Prophylaxis for GVHD included cyclosporine (1.5 mg/kg/IV from day -2 until day +7 and 3 mg/kg /IV/ from day +7) and methotrexate (10 mg/m² on day +1 and 6 mg/m² on days +3, +6). All of the 20 patients in the study who completed all 3 phases of the study were free from any transfusion. After hospital discharge, we followed patients in our post-HSCT clinic weekly for the first month and then every 2 weeks till day +100. Anthropometric factors such as age, sex, weight, height were also recorded.

Treatment related adverse events were graded using the National Cancer Institute (NCI) Common Toxicity Criteria (CTC). Acute GVHD (aGVHD) was graded according to standard criteria.[10,11]

Table 1. Characteristics of Patients

Parameter	Mean	SD	Minimum	Maximum
Age (y)	10.8	3.9	2	17
Age of diagnosis of BTM (y)	1	0.9	0.17	3
Age of start of chelation therapy (y)	3.2	1.3	2	6
Height (cm)	134	18	88	160
Weight (kg)	30	11	10	58
Ferritin (ng/mL)	2399	1397	1200	5100

Abbreviation: BTM, beta thalassemia major.

Lab Tests

Procedures

Serum samples from each participant were stored at -8ºC and analyzed as a batch at a central facility (EMRC laboratories, Tehran, Iran). IGF1 was measured by ELISA (IDS, UK) and Ferritin, T3, T4, TSH, LH, FSH, testosterone, estradiol, prolactin, cortisol were determined by ELISA (Monobind, USA). IBL kits (Germany) were used for measurement of serum ACTH.

Clonidine Stimulation Test

Patients fasted over-night. At the beginning of the test, an intravenous cannula was inserted into the cubital vein and the fasting sample was obtained. Patients took a single oral dose of clonidine, 4 μg/kg. Blood samples were withdrawn every 30 minutes. for GH levels at 30, 60, 90 and 120 minutes. Patients were checked for principle adverse effects of clonidine such as dry mouth, dizziness, hypotension (low blood pressure) and drowsiness.

Cosyntropin Test

Cortisol and ACTH levels measured at baseline (time

= 0). Subsequently, patients took a single IV dose of synthetic ACTH. Venous blood was collected at 30 and 60 minutes and cortisol levels were checked.

Diagnostic Criteria for Endocrine Disorders

1) Delayed puberty defined as lack of secondary sexual characteristic (no thelarche) after 13 years old in girls and (no increase of testes size) after 14 years old in boys.
2) Hypogonadotropic hypogonadism defined as low FSH, LH and estradiol (among females) and testosterone (among males).
3) Short stature in children was defined by height Z-score < -3.
4) GH deficiency confirmed, if short stature patients had a positive clonidine test (none of the GH results in blood samples found >10 ng/dL).
5) Low IGF1 defined as low abnormal serum IGF1 in comparison with age and sex matched controls in endocrine laboratory assessments.
6) Hypocortisolism defined as serum cortisol less than 18 μg/dL at 30 and/or 60 minutes after the synthetic ACTH injection.
7) Hypothyroidism defined as sub-clinical hypothyroidism defined as TSH between "5-10 MIu/mL" and TSH more than 10 defined as clinical hypothyroidism. Secondary hypothyroidism defined as "TSH normal and T4 in low levels".
8) Panhypopituitarism defined as co-existence of more than 2 central hormone deficiencies.

Statistical Analysis

Continuous variables were summarized as means (SD) and median (inter-quartile range). Categorical variables were summarized as numbers (percentages). We reported non-normal variables as median (inter-quartile range). Normal distribution of continuous variables was assessed using the Shapiro-Wilk test.

For finding correlation between dependent (IGF1, Prolactin, T3, T4, TSH, LH, FSH, testosterone for males and estradiol for females) and independent variables (corticosteroid use before HSCT and sex) the independent samples *t* test was used for comparison of means between the 2 groups of cases. We used the Mann-Whitney tests to compare independent samples for continuous variables without normal distribution.

All continuous variables, due to lack of normality (no parameter had normal distribution in all 3 phases) were compared using "test for several repeated samples".

Pearson's or Spearman's rho, were used for finding correlation between independent (age, ferritin) and dependent variables before HSCT. All inferences were based on a 2-tailed significance, with a threshold of $\alpha = 0.05$ for declaring significance. SPSS16 was used for statistical analysis.

Results

The mean (SD) age of patients was 10.8 (3.9) years old. Female to male ratio was 6:14. Tanner stages B0 and G0 were found in 13 cases and 11 cases, respectively. Stages B4 and G4 found only in 1 case.

Acute GVHD was found in 12 patients (6, grade I; 4, grade II; 1 grade III and 1, grade IV) and 4 patients (20%) experienced limited chronic GVHD. Fifteen out of 20 patients had history of corticosteroid therapy after HSCT. Before HSCT, delayed puberty (6 patients reached age of puberty), hypogonadotropic hypogonadism, GH deficiency, Low IGF1, short stature, hypocortisolism, hypothyroidism and panhypopituitarism was found in 10%, 20%, 25%, 55%, 40%, 15%, 10% and 15% of our patients, respectively. No case of secondary hypothyroidism was found.

Hypocortisolism after HSCT, due to corticosteroid use in patients, was not possible to judge. Prevalence of hypogonadotropic hypogonadism, Low IGF1, hypothyroidism and panhypopituitarism was 20%, 40%, 10% and 10% after 3 months, respectively (changes in prevalence of delayed puberty, GH deficiency, short stature after 3 months was not expectable). Results can be noted in Table 2.

We found no significant effect from HSCT on hormones of the hypothalamus-pituitary axis, except T3, TSH and estradiol ($P = 0.048$, 0.01, 0.001, respectively). Changes in absolute values of above hormones between, before, and after HSCT was not significant except T3, TSH and estradiol ($P = 0.005$, 0.024 and less than 0.001,

Table 2. Prevalence of Endocrine Disorders Before and After HSCT

Disorders	Before HSCT	1 Month After HSCT	3 Months After HSCT
Delayed puberty	2	-	-
Hypogonadotropic hypogonadism	4	4	4
GH deficiency	5	-	-
Low IGF1	11	7	8
Short stature	8	-	-
Hypocortisolism	3	-	-
Hypothyroidism	2	1	2

Abbreviation: HSCT, hematopoietic stem cell transplantation.

Table 3. Median of Endocrine Tests' Results Before and After HSCT

Parameters	Values		
	Phase 1	Phase 2	Phase 3
IGF1 (ng/mL)	0.6(-0.5)	0.01(-0.6)	0.01(-0.7)
Prolactin (ng/mL)	5.8(5.3)	8.7(-5.4)	7.2(-4.7)
FSH (mIU/mL)	1.6(1.8)	2.9(2.9)	3.0(5.1)
LH (mIU/mL)	0.8(0.3)	1.5(1.3)	0.8(1.8)
Testosterone (ng/mL)	0.5(0.8)	0.2(0.5)	0.1(0.4)
Estradiol* (pg/mL)	0.2(0.2)	0.5(0.4)	8.1(0.5)
T3* (ng/dL)	0.01(0.004)	0.01(-0.8)	0.01(-0.9)
T4 (µg/dL)	7.6(1.6)	7.6(1.8)	7.3(2.5)
TSH* (mIU/mL)	1.7(1.2)	2.0(1.5)	3.2(2.0)

Values are reported as median (75th-25th); * $P<0.05$.

respectively). Results can be noted in Table 3.

Age of diagnosis and start of chelating agents has no relation with hormones. Age and ferritin had a negative correlation with 30-minute cortisol level after the ACTH provocation test ($P=0.011$ and $P=0.044$). Age also had a negative correlation with 60-minute cortisol level after the ACTH provocation test ($P=0.026$). Before transplantation, ACTH had an upper level in boys ($P=0.005$). Corticosteroid use after BMT has negative correlation with T3, testosterone and estradiol after 3 months from BMT ($P=0.004$, $P=0.025$ and $P=0.028$). Corticosteroid use after BMT had positive relationship with IGF1 after 3 months from BMT ($P=0.005$).

Discussion

In our study, changes in prevalence of endocrine disorders in 3 months after HSCT was not found (Table 2). Of course, changes in prevalence of delayed puberty, GH deficiency, short stature after 3 months was not expectable. So, we think HSCT does not appear to have an overall positive or negative effect on the pituitary-hypothalamus axis in pediatric thalassemic patients in 3 months post-HSCT.

Thalassemia, as a group of blood diseases, is the most prevalent monogenic disease worldwide.[12] In the major beta form; the bone marrow makes inappropriate forms of beta chains of hemoglobin. So, patients need blood transfusion to live and hyper-transfusion leads to hemochromatosis.[5] By curing the main disease by HSCT, maybe different types of endocrine problems appear. Most, but not all of them, are consequences of transplantation conditioning with total body irradiation (this is not the case in patients in this study) and/or chemotherapy.

We found that HSCT lowers T3 and estradiol in females and increases TSH. Corticosteroid users had higher GH and lower T3. Male and female corticosteroid users had lower testosterone and estradiol, respectively. These findings are not surprising. Abnormal findings of thyroid function tests- called sick euthyroid syndrome- is common in the setting of some chronic and critical non-thyroidal illness (NTI) (e.g. bone marrow transplantation). This syndrome is known by low circulating thyroid hormones (T3 and T4) and sometimes higher TSH levels.[13] Finding lower estradiol level in females also may be caused, principally, by myeloablative drugs or corticosteroid use.[14,15] Corticosteroids lower secretion of insulin-like growth factor-I (IGF-1).[15] and may cause elevation of GH levels.[16] Reduction of testosterone levels in males and estradiol in females are also known phenomena after corticoid administration.[15,17]

Corticosteroids change plasma volume and thyroid hormones and thyroid hormone binding proteins, so may T3 level decrease.[18] Another reason of low T3 may be reduction in conversion of T4 to T3.[19] We found a significant positive correlation between ferritin levels (before HSCT) and T3 and T4 levels after HSCT. We also found older patients to have higher levels of FSH, LH and testosterone that is a general finding, but we did not find significant correlation between age and endocrine disorder and this may be due to a small sample size that is a limitation of our study and other studies with similar findings.[6]

Some investigators believe that HSCT patients- especially older ones- are at high risk for permanent gonadal dysfunction and consider myeloablative conditioning as the main cause.[3] We think the reason behind no change in prevalence of hypogonadotropic hypogonadism among our patients is their young age (with mean age of 0.8 ± 3.9 years old).

In this study, we did not find any significant correlation between gender, FSH and LH levels though other studies reported the contrary[1,2] and we have no explanation for this difference. In this study, prevalence of hypothyroidism was 10% and did not change after 3 months. In other studies, the prevalence was reported to be 11% and 20%.[3] Secondary adrenal insufficiency (due to prolonged steroid treatment for chronic GVHD) and impaired linear growth are also common findings in HSCT patients but due to our short follow-up, changes in their prevalence is not expected.

In summary, due to our lack of clear understanding, it is impossible to predict the exact time of change in hormone levels and the proper time of medical intervention after HSCT. Finding such answers is very important because, for example, most pediatric female patients may have amenorrhea and or insufficient levels of FSH or LH.[6] This means infertility in their adulthood and need for help to prevent and treat infertility in their future.[20]

Also it is not clear how much benefit can be obtained from hormone replacement therapy; nor which is

the correct replacement dose of hormones. So, such studies are important to help find the natural history of endocrine disorders in pediatric HSCT – especially thalassemic patients- and help patients to acquire quality of life after HSCT.

In conclusion, though considering out small sample size and short duration of study, it is difficult to reach any conclusion, we found out HSCT does not have any positive or negative impact on prevalence of the pituitary-hypothalamus axis disorders in pediatric thalassemic patients in short-term (3 months). Limitations of our study are a small sample size and a short follow-up period. For examining changes in endocrine disease rates among patients with thalassemia -due to HSCT, it is better to compare data with non-thalassemic HSCT patients and non-transplanted thalasemic patients. We hope these limitations can be overcome in our future studies.

Authors' Contribution

Study design: AAH, MRMT, BL, AG, MP, KA, ZH. Study conduct: AAH, MRMT, MB, ZH. Data collection: AAH, MRMT, MB, ZH. Data analysis: ZH. Data interpretation: AAH, MRMT, FM, ZH. Drafting of the manuscript: ZH, RM. Revising manuscript content: FM, MRMT. Approving final version of manuscript: MRMT, AAH. ZH takes responsibility for the integrity of the data analysis.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

Ethical Statement

This study was approved by the ethics committee of the Endocrinology and Metabolism Research Institute of Tehran University of Medical Sciences (EMRI of TUMS) and were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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