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Pituitary Iron Deposition and Endocrine Complications in Patients with β-Thalassemia: From Childhood to Adulthood

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ABSTRACT

The endocrinological complications are a great concern in transfusion-dependent β-thalassemia (β-thal) patients. The pituitary iron deposition is regarded as the main cause of hormonal changes in thalassemic patients. In this study, our aim was to explore the association between endocrinological complications and pituitary iron overload by magnetic resonance imaging (MRI). Fifty transfusion-dependent thalassemia (TDT) patients were recruited for the study. Pituitary MRIs of patients were taken using a 1.5 Tesla Philips MRI machine. There was at least one clinical endocrine complication in two of three patients. The iron accumulation was moderate in the liver (60.0%) and was mild in hypophysis (16.0%) and in heart (8.0%). The hypogonadism and diabetes mellitus (DM) were not seen with a significantly increased pituitary iron burden. The hypogonadism was related to cardiac iron deposition ($p = 0.04$). The short stature was associated with a hepatic iron overload ($p = 0.05$). The conventional follow-up of patients with TDT might be inadequate and screening of patients with MRI of hypophysis along with heart and liver leads to better results.

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Endocrinological complications; magnetic resonance imaging (MRI); pituitary iron; transfusion-dependent thalassemia (TDT)

Introduction

Thalassemia is one of the most prevalent genetic diseases among the single gene disorders. Regular chelation therapy and blood transfusion programs now extend the life-span of the patients with β-thalassemia (β-thal) [1]. As the life expectancy of the transfusion-dependent thalassemia (TDT) patients is increased, previously disregarded endocrinological problems have come into prominence [1]. Short stature, delayed puberty and hypogonadism, bone diseases such as osteoporosis, diabetes mellitus (DM), hypothyroidism and hypoparathyroidism are the most common complications among β-thal patients [2]. However, the rate of these endocrine complications has been decreased by strict chelation therapy and early treatment with appropriate agents [3].

The pituitary iron accumulation can cause dysfunction of hypophysis and hormonal changes in thalassemic patients. This study aimed to research the endocrinological complications of TDT patients and to investigate the correlation between complications and iron overload in hypophysis, liver and heart.

Materials and methods

This research is a cross-sectional study, performed at the Thalassemia Center, Istanbul Faculty of Medicine, Istanbul, Turkey. Patients who were willing to participate in the study had undergone magnetic resonance imaging (MRI) examination at the Radiology Department, Istanbul Faculty of Medicine, Istanbul, Turkey between March 2016 and May December 2017. The radiology clinic is used as the central clinic for heart, liver and pituitary iron deposition of patients coming from all over Istanbul. Therefore, patients followed-up only by the Istanbul Medical Faculty were accepted for the study to maintain integrity and provide homogeneity. This study was approved by the local university Ethics Committee [protocol number 2016413]. A signed informed consent form was obtained from all participants.

The 23 (46.0%) female and 27 (54.0%) male patients (29.5 ± 11.5 years, median 30 years with a range of 11 to 51 years) with TDT, in a regular transfusion program and receiving chelation treatment, were included in the study. Patients were willing to participate and accepted undergoing MRI of the hypophysis during routine scans of heart and liver.

Patients were followed from the time of diagnosis. The median duration of follow-up was 28 years. Mean disease duration was 27.5 ± 11.6 years (median 28 years) and mean age of diagnosis was 23.9 ± 26.0 months (median 12 months). The mean age of starting regular transfusions was

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32.1 ± 35.9 months (median 12 months), while the mean age of starting iron chelation was 111.1 ± 94.2 months (median 84 months). The mean age of splenectomy was 175.0 ± 85.3 months (median 167 months).

All patients received blood transfusions every 3 to 4 weeks (mean transfusion number 17.1 ± 4.1 annually) in order to maintain a hemoglobin (Hb) level between 9.0 and 10.0 g/dL. Nearly half of the patients' parents had consanguineous marriages and half of the patients did not have thalassemic facial appearance. Mean body mass index (BMI) was 21.9 ± 3.2k g/m^2 (median: 21 kg/m^2). Mean height was 162.7 ± 11.3 cm and mean weight was 58.6 ± 10.8 kg. Mean first menstrual cycle age was 16.6 ± 2.9 years for girls. Half of females had irregular menstrual cycles. One in three patients had late puberty.

Forty (80.0%) patients were taking deferasirox (DFX), nine patients (18.0%) were taking deferiprone (DFP) and one patient was taking both DFP and DFX. There was no problem in compliance with chelation therapy. Twenty-eight (56.0%) patients had undergone splenectomy operation (Table 1).

A cardiac iron overload was defined as a value of <20.0 ms on MRI T2* [4]; a hepatic iron overload was defined as a value of <6.3 ms on MRI T2* [5], and a pituitary iron overload was defined as less than <5.9 ms on MRI T2* [6]. The super conductor magnetic resonance imaging (MRI) device with a main magnetic field force of 1.5 Tesla (Achieva 1.5 T A-series; Philips, Eindhoven, The Netherlands) and 8-channel SENSE-head coil was used in acquisitions. All imaging acquisitions were conducted with a special protocol created for examining the iron loading in the pituitary gland of β-thal patients. First, imaging was performed with a cranium-oriented coronal T2-weighted turbo spin echo (TSE) sequence covering the whole pituitary gland for morphological examination. Imaging parameters were 2 mm slice thickness with 15 slices; slice interval as 1 mm; echo time (TE): 100.0 ms; field of view (FOV): 240 × 240 mm; repetition time (TR): 5058.0 ms; number of signal averages (NSAs): 2.

Table 1. Clinical and laboratory characteristics of the patients.

Characteristics	TDT ($n = 50$)	Median
Gender (females)	23 (46.0%)	
Disease duration (mean ± SD years)	27.5 ± 11.6	28.0
Age (mean ± SD years)	29.5 ± 11.5	30.0
Age at diagnosis (mean ± SD months)	23.9 ± 26.0	12.0
Age at starting regular transfusions (mean ± SD months)	32.1 ± 35.9	12.0
Age at starting chelation (mean ± SD months)	111.1 ± 94.2	84.0
Age when splenectomized (mean ± SD months)	175.0 ± 85.3	167.0
Transfusion number/year (mean ± SD)	17.1 ± 4.1	
Body mass index (mean ± SD kg/m^2)	29.9 ± 3.2	21.0
Splenectomy (yes)	28 (56.0%)	
Chelation therapy:		
DFX	40 (80.0%)	
DFP	9 (18.0%)	
DFX + DFP	1 (2.0%)	
Endocrine complications:		
Osteoporosis	26 (52.0%)	
Hypogonadism	14 (28.0%)	
Diabetes mellitus	10 (20.0%)	
Short stature	9 (18.0%)	
Hypothyroidism	9 (18.0%)	
Hypoparathyroidism	4 (8.0%)	

TDT: transfusion-dependent thalassemia; DFX: deferasirox; DFP: deferiprone.

The T2* maps were generated in coronal, axial and sagittal plans using multiple gradient-echo sequences [GRE-weighted fast field echo (FFE) sequence] with different TEs. Parameters of imaging protocol were slice thickness: 1 mm, slice interval: 1 mm, matrix: 195 × 256; FOV: 240 × 240 mm; TR: 305.0-310.0 ms; flip angle: 30 °. The range of TE was 8.0-15.0 ms, and delta TE was 1.0 ms. The T2* was calculated automatically using the formula = Ke $^{-TE/T2*}$, where Ke is a constant, TE and y represent the TE and image consecutive signal intensities. The R2* values were calculated using 1/T2* formula.

Seven slices crossing the same slice plan in 7-TE FFE images were exported as digital imaging and communications in medicine (DICOM) and transferred to a software iron analysis software (Thalassemia Tools; Cardiovascular Imaging Solutions, London, UK) developed to calculate iron accumulation. Pituitary T2* values measured over T2* map using the region of interest (ROI) (3 mm^2 area) in adenohypophysis. Care was taken not to include vascular structures and neurohypophysis in the ROI and T2*, and R2* values were calculated.

Patients were followed at the endocrinology polyclinic and definitions were made according to clinical guidelines [7]. Short stature was considered as height measurement lower than −2SD.

Hypogonadism was considered as non-development of secondary sex characters at 14 years of age in boys and 13 years of age in girls. Gonadal development defined as lack of breast development in girls and testicle volume lower than <4 ml in boys, and laboratory definitions were luteinizing hormone (LH) <0.3 mU/mL in girls, testosterone <20.0 ng/dL in boys and estradiol <10.0 pg/mL in women.

Diabetes mellitus was determined as fasting glucose >126.0 mg/dL and blood sugar >200.0 mg/dL at any time. Hypothyroidism was defined as deficiency of free thyroxin (fT4) with high (primary) or low to normal thyroid stimulating hormone (TSH) (secondary). Hypoparathyroidism was defined as low parathyroid hormone (PTH) level with hypocalcemia. Osteoporosis was diagnosed with both fracture history and low bone mineral density (T score below −2.5SD or Z score below −2SD).

Statistical analyses

The Statistical Package for the Social Sciences (SPSS) V21.0 (IBM Corporation, Armonk, NY, USA or internet address) software was used for statistical analyses. The Mann Whitney U test was performed to compare two groups of variables and quantitative data. Correlation analysis was done for revealing of the inter-variable relations. Screening tests [sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)] and receiver operating characteristic (ROC) curve analysis was performed to determine cutoff values. A p value of <0.05 was considered to be significant.

Results

One or more clinical endocrine complications were detected in 62.0% of the participants ($n = 31$). The rate of complications

in descending order were osteoporosis 52.0% ($n = 26$), hypogonadism 28.0% ($n = 14$), DM 20.0% ($n = 10$), short stature 18.0% ($n = 9$), primary hypothyroidism 18.0% ($n = 9$) and hypoparathyroidism 8.0% ($n = 4$) (Table 1).

The mean parathyroid hormone (PTH) level was 23.9 ± 18.7 pg/mL and mean 25 OH vitamin D level was 35.5 ± 19.7 ng/ml. Forty-two percent ($n = 21$) of patients had vitamin D insufficiency (<30 ng/mL). The mean fasting blood glucose was 100.7 ± 28.5 mg/dL and mean insulin level was 10.2 ± 6.6 μU/mL. The mean TSH level was 3.6 ± 2.7 mIU/L and mean fT4 was 15.7 ± 3.2 pmol/L. The mean insulin-like growth factor 1 (IGF-1) level was 150.2 ± 128.4 ng/mL. The mean estrogen level in females was 38.6 ± 22.9 pg/mL, while mean testosterone level in males was 5.6 ± 7.0 ng/mL.

The mean serum ferritin level was 1791.7 ± 1699.4 ng/mL (range 365.0-9851.0 ng/mL). Sixty-two percent of patients had a higher serum ferritin level than 1000.0 ng/mL. Patients using DFX ($n = 40$) had slightly lower levels of ferritin (median: 1149.0 *vs.* 1872.0 ng/mL, $p = 0.08$) and significantly higher cardiac T2* values (median: 39.4 *vs.* 25.9 ms, $p = 0.050$) compared to patients using DFP ($n = 9$).

In pituitary MRI, the mean R2* value was 91.8 ± 103.2 Hz (median 50.4 Hz) and the mean T2* value was 32.1 ± 39.1 ms (median 19.3 ms). Eight patients (16.0%) had iron overload in pituitary (lower T2* than 5.9 ms). Patients with endocrine complications had a lower mean pituitary T2* value (31.2 *vs.* 33.6 ms, $p = 0.83$) (Table 2). We found a positive significant correlation between ferritin level and pituitary R2* ($r = 0.45$, $p < 0.01$), however, there was a slight negative correlation between ferritin level and pituitary T2* value ($r = -0.25$, $p = 0.07$). Patients with a ferritin level higher than 1000.0 ng/mL also had significantly increased pituitary R2* value (122.3 *vs.* 46.2, $p < 0.01$). We also found a positive significant correlation between pituitary R2* and liver iron concentration (LIC), cardiac T2* and BMI ($p = 0.02$, $p = 0.04$, $p = 0.01$, respectively) and a slight positive correlation with hepatic T2* ($p = 0.06$).

Patients with hypogonadism had an insignificantly higher value of pituitary R2* (131.0 *vs.* 80.7 Hz, $p = 0.13$). They also had a high rate (21.0%) of cardiac iron overload ($p = 0.04$). Patients with DM also had an insignificantly higher value of pituitary R2*(109.2 *vs.* 87.4 Hz, $p = 0.35$). Patients with short stature showed significantly escalated LICs (median LIC: 10.6 *vs.*4.6 mg/g, $p = 0.05$) and 89.0% of them had hepatic iron overload ($p = 0.05$) (Tables 3 and 4).

Patients using DFP had an insignificantly higher value of pituitary R2* (135.0 *vs.* 81.0 Hz, $p = 0.14$). Patients who had been splenectomized also had an insignificantly higher value of pituitary R2* (107.0 *vs.* 73.9 Hz, $p = 0.26$). The cutoff point for ferritin level was 1498.5 ng/mL [69.0% sensitivity and 72.0% specificity, with 0.66 area under curve (AUC)] for prediction of hypogonadism, and 1469.0 ng/mL for DM and 1428.0 ng/mL for hypothyroidism ($p = 0.03$).

The mean cardiac T2* value was 37.2 ± 13.7 ms and mean hepatic T2* level was found to be 6.8 ± 5.7 ms. The mean LIC value was detected to be 8.1 ± 6.7 mg/g. Eighty-four percent ($n = 42$) of patients did not have pituitary iron burden (*i.e.* pituitary T2* >5.9 ms), 90.0% of patients ($n = 45$) did not have cardiac iron burden (*i.e.* cardiac T2* >20.0 ms), while 38.0% of patients ($n = 19$) were free of hepatic iron burden (*i.e.* hepatic T2* >6.3 ms).

Table 2. Evaluation of iron accumulation based on clinical endocrine complications.

Characteristic (mean ± SD) (median)	Thalassemia without Endocrine Complications ($n = 19$)	Thalassemia with Endocrine Complications ($n = 31$)	p Value
Pituitary R2* Hz	79.1 ± 94.7 (46.0)	99.6 ± 108.8 (56.1)	0.50
Pituitary T2* ms	33.6 ± 40.9 (20.5)	31.2 ± 38.6 (17.8)	0.83
Cardiac T2* ms	36.5 ± 9.6 (38.0)	37.6 ± 16.1 (39.7)	0.78
Hepatic T2* ms	7.1 ± 5.2 (5.7)	6.7 ± 6.0 (3.1)	0.47
LIC (mg/g)	6.9 ± 6.2 (4.6)	8.8 ± 7.1 (8.3)	0.33

LIC: liver iron concentration.

Table 3. Evaluation of iron accumulation according to endocrine complications. (Results are presented as mean ± SD.).

Clinical Endocrine Complications	Pituitary R2* Hz (median)	Pituitary T2* ms (median)	Cardiac T2* ms (median)	Hepatic T2*ms (median)	LIC (mg/g) (median)	p Value
Hypogonadism with ($n = 14$)	131.0 ± 29.3 (80.9)	27.6 ± 42.6 (12.9)	35.2 ± 21.3 (36.5)	6.4 ± 5.7 (4.1)	10.4 ± 8.5 (6.4)	insignificant
without ($n = 33$)	80.7 ± 93.4 (48.8)	33.9 ± 33.6 (12.9)	.7 ± 93.3 (39.0)	7.3 ± 5.9 (5.6)	7.4 ± 6.0 (4.6)	
Diabetes with ($n = 10$)	109.2 ± 93.3 (80.9)	21.8 ± 26.6 (12.9)	36.6 ± 15.5 (39.9)	8.3 ± 7.8 (4.7)	9.4 ± 8.0 (7.1)	insignificant
without ($n = 40$)	87.4 ± 10.2 (49.2)	34.7 ± 46.5 (19.9)	37.3 ± 13.5 (38.1)	6.5 ± 5.1 (5.1)	7.7 ± 6.5 (5.1)	
Short stature with ($n = 9$)	145.5 ± 135.3 (80.1)	17.8 ± 17.2 (12.5)	37.5 ± 20.6 (42.1)	3.6 ± 3.4 (2.4)	12.0 ± 7.6 (10.6)	0.01[a]; 0.05[a]
without ($n = 41$)	80.0 ± 92.7 (48.8)	35.2 ± 3.89 (20.2)	37.1 ± 12.4 (38.2)	7.6 ± 5.9 (5.7)	7.2 ± 6.3 (4.6)	

LIC: liver iron concentration.
[a]The p value shows specific that the hepatic T2* and LIC values differ.

Table 4. Endocrine complications and body iron overload.

Endocrine complications ($n = 31$)	Pituitary iron overload ($n = 8$)	Cardiac iron overload ($n = 4$)	Hepatic iron overload ($n = 30$)
Hypogonadism ($n = 14$)	21.0%	21.0% ($p = 0.04$; $\chi^2 = 4.1$)[a]	64.0%
Short stature ($n = 9$)	33.0%	11.0%	89.0% ($p = 0.05$; $\chi^2 = 3.5$)[b]
Hypothyroidism ($n = 9$)	22.0%	11.0%	67.0%
DM ($n = 10$)	20.0%	10.0%	50.0%
Osteoporosis ($n = 26$)	23.0%	12.0%	60.0%

DM: diabetes mellitus.
[a]There are a total of four patients with cardiac iron burden (cardiac T2* <20.0 ms) and three of them had hypogonadism. On the other hand one in five patients with hypogonadism had cardiac iron burden ($p = 0.04$; $\chi^2 = 4.1$).
[b]There are a total of 30 patients with hepatic iron burden (hepatic T2* <6.3 ms) and eight of them had short stature. On the other hand, eight of the nine patients with short stature had hepatic iron burden ($p = 0.05$; $\chi^2 = 3.5$).

No significant correlation was found between pituitary iron deposition and splenectomy, chelation type, gender, age and disease duration. On the other hand, positive correlation between hepatic T2* and cardiac T2* were determined ($p = 0.005$). Cardiac T2* was also slightly and negatively associated with BMI ($p = 0.08$, $r = -0.25$).

Discussion

In this study, we showed that at least one clinical endocrine complication was detected in two of three patients with TDT. The iron deposition was moderate in liver (60.0%), and was mild in hypophysis (16.0%) and in heart (8.0%). Ferritin level of 1500.0 ng/mL was shown as a threshold for endocrine complications (hypogonadism, DM, hypothyroidism). In previous studies of thalassemic patients, it has been shown that the rate of endocrinological complications were apparent, most frequently being hypogonadism, short stature, impaired glucose intolerance and DM and hypothyroidism [8–13]. It was revealed that high ferritin levels negatively affected pubertal development and better chelation therapy was found to be an important factor in puberty onset of girls [14]. In accordance with previous studies, we also found similar complication rates with common hypogonadism in patients with β-thal.

There was a positively significant correlation between pituitary R2* value and ferritin level, LIC, cardiac T2* and BMI. Diabetes mellitus and hypogonadism was not seen significantly in patients with pituitary iron overload. Hypogonadism was found to be related with cardiac iron burden. Patients with short stature had significantly escalated LIC. A significantly positive correlation between cardiac and hepatic iron overload was detected. The pituitary iron deposition shown by MRI was studied earlier in thalassemic patients [15] and standardized according to a healthy population by Noetzli *et al.* [16]. In that study, they measured the T2 and R2 values (not T2*/R2*) and pituitary median T2 value was determined as 88.9 ms and median R2 value was determined as 11.3 Hz. Another imaging study [17] showed 14.9 ms mean pituitary T2* value in β-thal major (β-TM) patients. The Au *et al.* [6] study on β-TM patients and an acceptable iron burden on pituitary as MRI T2* value lower than 5.9 ms.

Bozdag *et al.* [18] found significantly higher pituitary iron accumulation in β-TM with hypogonadism (18.0 Hz) than both healthy subjects (10.0 Hz) and β-TM patients without hypogonadism (12.0 Hz). They revealed a threshold level of 14.1 Hz for the pituitary R2 in terms of hypogonadism. In our study, we measured the pituitary R2* value (not R2 value) and 50.4 Hz median R2* value and 19.3 ms median T2* value was obtained. Although patients with hypogonadism and DM had more iron burden in hypophysis, this was not statistically significant in our study.

Pituitary cells are very sensitive to iron and any abnormal accumulation can disturb its function [19]. Hypogonadism is a typical sample of iron deposition in thalassemic patients. The rate of hypogonadism is quite high, more than 50.0% in thalassemic patients worldwide. The possible pathophysiology is direct iron toxicity, *i.e.* iron overload in anterior pituitary or in gonads, chronic anemia, and development of reactive oxygen species (ROS) [20]. The evaluation of patients at prepuberty is difficult because of pituitary gonadal axis immaturity [21]. Noetzli *et al.* [16] determined that 25.0% of the β-thal patients had a serious iron accumulation in the pituitary gland during the first 10 years of life and suggested that it was appropriate to perform pituitary MRI for β-TM patients older than 7 years because an early-diagnosed hypogonadism can be reversed with suitable treatment. In our study, nearly one-third of patients were hypogonadic and a slightly high iron overload was seen in the pituitary gland. It was previously shown that a regular transfusion programs and chelation administration can diminish the rate of hypogonadism in patients with β-thal. Therefore, a close follow-up of patients with both serum parameters and MRIs might be an important step for alleviation of endocrine symptoms.

Diabetes mellitus is another major complication in β-thal, with a rating of approximately 20.0–30.0% [22]. The possible pathophysiology might be direct iron toxicity, *i.e.* iron overload in pancreatic tissue results in diminished insulin secretion, liver dysfunction and ROS that yields insulin resistance [23]. A combining of insulin resistance and insulin deficiency can form a large scale of DM in thalassemic patients [24]. Therefore, pancreatic and liver iron burden is evidently associated with DM in patients with β-thal [20]. It might be supposed that these patients likely had pancreatic iron overload that we plan to investigate in next study. On the other hand, it might be speculated that the pituitary iron accumulation can disturb the neuroendocrine function of hypophysis, and thus, blood sugar metabolisms can be deteriorated.

The complication of short stature can also be a result of chronic disorder, deficiency of growth hormone, deficiency of growth factors owing to liver dysfunction, and disturbed bone metabolism [25]. The synthetic capacity of liver for growth factors might diminish by high iron overload [26]. In this study, we also showed a significant correlation between short stature and liver iron burden.

The cardiac iron burden is one of the most important reasons of death in patients with β-thal [27]. Strict chelation therapies can reverse cardiomyopathy [28]. Recently, DFX was found to be effective for cardiac iron burden [29]. In our recent study, up to 20.0% of TDT patients were under cardiac risk in terms of iron burden [30]. In our current study, we showed mild cardiac iron involvement (10.0% of patients) and patients using DFX were more favorable in terms of cardiac iron overload compared to the DFP group. The ferritin value in the DFX group was also lower. On the other hand, three of four patients with cardiac iron burden had hypogonadism. This result might indicate that the iron overload in extra hepatic organs might be related to endocrine complications. As chelation of iron from the extra hepatic tissue is slower than from hepatic tissue, the heart might very well be a candidate for close follow-up of endocrine complications in thalassemic patients.

We found acceptable rates for cardiac, liver and hypophysis iron deposition. The lack of the same ethnic control group, and a restricted number of patients, are our main

limitations to draw a definitive conclusion. A larger cohort study with a control group would yield better results.

Conclusions

Endocrine complications have gradually decreased during the past 10 years with effective chelation therapy programs. Monitoring only ferritin levels might not be sufficient. It can be speculated that routine MRI acquisition can be suitable to detect endocrine complications, to assess iron accumulation in the organs and determine the impact of an effective chelation therapy program.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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