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Magnetic Resonance Imaging Versus Serum Iron Status as Diagnostic Tools for Pituitary Iron Overload in Children with Beta Thalassemia

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Authors' contributions

This work was carried out in collaboration among all authors. Author LMM designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors NMH, RAEl-S, ASEl-B and MREL-S managed the analyses of the study. Author AAH managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Thalassemia is a common genetic disorder associated with endocrine disorders. Iron deposition may start in the anterior pituitary gland, but clinical signs are usually not evident until puberty. Aim of the study was to evaluate pituitary iron overload in children with β thalassemia using MRI T2* and correlate MRI T2* and biochemical markers of iron overload with pituitary hormones.
Patients and Methods: This study was carried out on 30 children with β-thalassemia major (19 females and 11 males) with their age ranging from 10 - 18 years and mean age value of 12.8 ± 2.4 and 30 healthy children of matched age and sex as controls in the period from September 2018 to September 2019. For all patients the following were done: complete clinical evaluation including anthropometric data and Tanner staging, laboratory investigations including serum iron status, thyroid function, basal and growth hormone provocation test by clonidine, Follicle stimulating hormone (FSH) , Luteinizing hormone (LH) , and pituitary MRI T2*.

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Results: Weight, Z score of weight, height, Z score of height and Body mass index (BMI) were found significantly lower in patients compared with controls. Patients had delayed puberty compared with controls. Pituitary MRI T2* was found significantly lower in patients compared with controls (P=0.001). FSH, LH, and provocative growth hormone levels were found significantly lower in patients compared to controls (p <0.001). Serum ferritin & iron were found significantly higher in patients than controls (P<0.001). Significant negative correlations were found between serum ferritin and Weight, Height, Z score of Weight, Z score of Height, BMI and pituitary hormones. Significant negative correlations were found between Pituitary MRI T2* and serum ferritin. Significant positive correlations were found between Pituitary MRI T2* and Weight, Height, Z score of Weight, Z score of Height and pituitary hormons. The pituitary T2* carried the sensitivity of 80% ,100% and 100% and specificity of 70% ,83.3% and 100% for predicting GH hormone abnormality, LH and FSH respecetively.

Conclusions: There were a significant positive correlations between pituitary MRI T2*and anthropometric measurement and pituitary hormones of studied patients. There was a significant negative correlation between Pituitary T2* and serum ferritin. Pituitary iron overload can be detected by MRI T2* which is a diagnostic tool in detecting pituitary iron overload with subsequent effect on hormonal secretion especially growth hormone.

Recommendations: Children with thalassemia should undergo meticulous follow up regarding regular blood transfusion, regular iron chelators in a proper manner and doses and routine use of MRI T2* in the evaluation of pituitary iron overload before irreversible damage occur in the pituitary gland.

Keywords: Thalassemia; iron overload; pituitary MRI T2.*

1. INTRODUCTION

Thalassemia is a category of genetic disorders characterized by impairment of globin-chain synthesis [1].

The human body lacks active mechanism to excrete excess iron, therefore repeated blood transfusions lead to iron overload in these patients. Excess iron can deposit in body organs particularly in pancreas, liver, pituitary, and the heart. To avoid iron overload, thalassemia patients are treated with iron chelators concomitantly with the blood transfusions [2].

Labile plasma iron (LPI) or reactive plasma iron (RPI) reflects the potentially harmful source of circulating iron as it produces oxygen radical species that can destroy cell membranes and also intracellular organelles (including mitochondria and nuclei) and DNA [3].

Iron deposition may begin in the anterior pituitary gland in the first decade of life, but clinical symptoms are usually not apparent before puberty. Only reduced gonadotropin reserve was observed at the earlier stage, with intact gonadotropin pulse. Until hypogonadism occurs an asymptomatic process of pituitary siderosis may occur [4].

Disorders of endocrinopathy caused by frequent blood transfusions and iron overload are of greater concern in large patients with thalassemia. They are the second leading cause of mortality in this population, after heart disorder [5].

There are three major clinical manifestations of the hypothalamic–pituitary– gonadal axis derangement (HPG) in TM, including delayed puberty, arrested puberty and hypogonadism [4].

Hypogonadotropic hypogonadism in thalassemia is associated not only with iron toxicity on gonadotropic cells, but also with adipose tissue and leptin resulting in impaired leptin synthesis and decreased its physiological role in sexual maturation and fertility as leptin significantly increases in early puberty and stimulates hypothalamic pituitary-gonadal axis [6].

1.2 Aim of the Work

The aim of this work was to evaluate pituitary iron overload in children with β thalassemia using MRI T2* and correlate MRI T2* and biochemical markers of iron overload with pituitary hormones.

2. PATIENTS AND METHODS

This case control study was carried out after approval from ethical committee of research center of Tanta University permission number 32211/03/18 and obtaining written consents from

the parents of all children included in this study and was conducted on 30 children with transfusion dependent β-thalassemia major including 19 females and 11 males with their age ranging from 10 - 18 years and mean age value of 12.8 ± 2.4 who attended to Hematology Unit, Pediatric Department, Tanta University Hospital in the period from September 2018 to September 2019 and 30 healthy children of matched age and sex as a control group .

2.1 Inclusion Criteria

Children with transfusion dependent β-Thalassemia major aged 10 - 18 years.

2.2 Exclusion Criteria

Children with thalassemia combined with other chronic hemolytic anemias as sickle thalassemia.

Children with β- thalassemia with contraindication to MRI as prosthetic valve, and dental prosthesis.

2.3 All Patients in this Study were Subjected to the Following

1. Complete history taking with special account on: consanguinity between parents, family history of thalassemia, age of diagnosis of thalassemia, frequency of blood transfusion and iron chelation therapy (types and regularity).
2. Thorough clinical examination with special account on pallor, jaundice, mongoloid facies, , hepatomegaly, splenomegaly or splenectomy, anthropometric measurements including body weight , height ,body mass index (BMI) and Tanner staging for assessment of puberty.
3. Laboratory investigations;

Specimen collection and preparation:

Ten ml of venous postprandial pre-transfusion blood were collected using sterile needles through gentle venipuncture after sterilization of puncture site and were classified in to ; 2 ml on 20 uL EDTA for CBC including differential WBCs count which was done on Leishman stained blood smear with evaluation using ERMA PCE-210 N cell – counter' [7] and HPLC [8] and 3 ml in a plain tube that was allowed for clotting in a water bath at 37ºc. After clotting, centrifugation was done at 1500x for 10 minutes. Separated serum was collected in three tubes. The 1st tube for assessment of serum growth hormone, GH provocation test by clonidine [9,10] , the 2 nd tube for measurement of liver and kidney functions [11] and The 3rd part for measurement of serum iron, total iron binding capacity [12], serum ferritin [13], Thyroid function (free T3, free T4, TSH), FSH and LH [14].

4. Radiological Investigations including: Assessment of bone age by Greulich and Pyle method [15] and Pituitary MRI (MRI T2*) [16].
5. Chelation Therapy in studied patients:

Deferasirox alone in a dose of 20-30 mg/kg/day once daily before meals [17], or Desferrioxamine alone 20-40 mg/kg/day for 6 days /week but in patients with persistently high serum ferritin levels above 3000 ng/ml, Deferasirox is combined with Desferrioxamine in a dose of 20-40 mg/kg/day for 10 days per month either by subcutaneous infusion using infusion pump in 8-12 hours/day or by continuous intravenous infusion for 8-10 hours/day (combined chelation therapy [18].

2.4 Statistics

Statistical analysis of the present study was conducted, using mean, standard error, student t- test, Chi-square, Linear Correlation Coefficient tests by SPSS V17.

3. RESULTS

Weight, Z score of weight, height, Z score of height and body mass index was significantly lower in patients compared with control group (Table 1).

Delayed puberty was found in patients compared with control group according to Tanner staging. Significantly higher prevalence of delayed menstruation (primary amenorrhea) was found in female patients compared with control group (Table 1).

Pallor and jaundice were the most common presenting symptoms in thalassemic patients, while hepatomegaly and spleenectomy were the most common signs (Table 2).

Microcytic hypochromic anemia with reticulocytosis was found in studied patients with thalassemia. Total leucocytic count and platelet

count were significantly higher in patients than control group (Table 3).

Serum ferritin and serum iron were significantly higher, while TIBC was significantly lower in patients than control group (Table 3).

Serum growth hormone, FSH and LH were significantly lower in patients than controls (Table 4).

Statistically significantly lower level of pituitary T2* was found in patients compared to controls (Table 4).

Statistically significant negative correlation was found between serum ferritin with weight, height, BMI, Z score of height and Z score of weight and bone age (Table 5).

Statistically significant negative correlation was found between serum ferritin with FSH, LH and GH (Table 5 and Fig. 1).

Statistically significant negative correlation was found between pituitary T2* with serum ferritin (Fig. 2).

Statistically significant positive correlation was found between pituitary T2* with weight, height, BMI, Z score of height and Z score of weight (Table 5).

Statistically significant positive correlation was found between pituitary T2* with ferritin, FSH, LH and growth hormone (Table 5 and Fig. 3).

No statistically significant correlation was found between pituitary T2* with bone age (Table 4).

Significant negative correlation was found between serum ferritin and growth hormone of thalassemic patients (Table 5).

Non-significant difference was found between patients and controls as regard TSH, free T3 ad free T4 levels (Table 4).

The pituitary T2* carried the sensitivity of 80% ,100% and 100% and specificity of 70% ,83.3% and 100% for predicting GH hormone abnormality, LH and FSH respecetively (Table 6).

Table 1. Demographic data, anthropometric measurements and Tanner staging in studied groups

parameters	Patients (n=30)	Controls (n=30)	t or X2	P-value
Age(years)				
Range	10 -18	10-18	- 0.494	0.623
Mean ±SD	12.8±2.4	13.1±2.3		
Weight (kg)				
Range	26 - 48	32.87 ± 5.26	-9.847	<0.001*
Mean ±SD	40 - 77	52.30 ± 9.44		
Z score Weight				
Range	-3.5 - 0.6	-1.10 ± 1.14	-14.716	<0.001*
Mean ±SD	1 - 4	2.70 ± 0.84		
Height (cm)				
Range	125 – 155.5	136.95 ± 7.73	-12.203	<0.001*
Mean ±SD	145 - 169	158.60 ± 5.89		
Z score Height				
Range	- 4 – 1.5	-1.60 ± 1.66	-12.592	<0.001*
Mean ±SD	1 - 4	2.67 ± 0.83		
BMI (kg/m2)				
Range	13.6 – 21.3	17.03 ± 1.97	-8.451	<0.001*
Mean ±SD	18.6 - 24	21.22 ± 1.88		
Tanner Stage				
Stage I Stage II Stage	9 (30%)	3 (10%)	28.932	<0.001*
III Stage IV Stage V	13 (43.3%)	5 (16.7%)		
	6 (20%)	5 (16.7%)		
	2 (6.7%)	7 (23.3%)		
	0 (0%)	10 (33.3%)		

** Significant difference (P < 0.05)*

Table 2. Clinical data, chelation therapy and frequency of blood transfusion in studied patients

Parameters	Patients (n=30)
Clinical data	
Pallor	30 (100%)
Jaundice	30 (100%)
Hepatomegaly	30 (100%)
Splenectomy	30 (100%)
Mongoloid Facies	30 (100%)
Types of iron chelators	
SC Desferroxamine (Desferal)	7 (23 %)
Oral Deferasirox (Exjade)	9 (30 %)
Combined chelation therapy	14 (46.7 %)
Regularity of iron chelators	
Regular	14 (46.7%)
Irregular	16 (53.3 %)
Frequency of blood transfusion	
Every 2 Weeks	5 (16.7 %)
Every 3 Weeks	10 (33.3 %)
Every 4 Weeks	9 (30 %)
Every >4 Weeks	6 (20 %)

Table 3. Comparison between patients and controls as regard pre-transfusion complete blood count and iron profile

Measure		Patients (n=30)	Controls (n=30)	t or X2	P value
Hemoglobin	Range	5 - 8	11 - 13.5		
(gm/dl)	Mean±SD	6.3 ± 1.1	11.8± 0.6	- 19.401	0.001*
RBCs	Range	1.7 – 2.7	3.5 – 5		
(million/mm3)	Mean±SD	2.1 ± 0.4	4.3 ± 0.4	-17.115	0.001*
	Range	15 – 24	33 – 39		
Hematocrit (%)	Mean±SD	18.9 ± 3.2	35 ± 1.7	-19.450	0.001*
	Range	50 -70	79 – 93		
MCV (fL)	Mean±SD	52 ± 12.2	85.9 ± 4	-11.510	0.001*
	Range	20 -26	28- 32		
MCH (pg)	Mean±SD	21.8 ± 2.5	30.6± 1.7	-12.807	0.001*
	Range	30 -34	31 -36		
MCHC (%)	Mean±SD	32.2 ± 1	32.9 ± 1.3	-1.965	0. 737
Retics (%)	Range	3 – 7	0.7 – 2		
	Mean±SD	5.3 ± 1.2	1.3 ± 0.5	13.108	0.001*
Platelets	Range	178 -555	150 -453		
(thousands/mm3)	Mean±SD	336 ± 108.6	253.9± 95.8	3.129	0.003*
WBCs	Range	4 – 12	4 – 9.876		
(thousands/m m3)	Mean±SD	7.36± 24.53	5.89± 16.21	2.724	0.009*
Serum Ferritin	Range	2000 - 9876	40 – 321		
(ng/ml)	Mean±SD	4907.6±2288.9	150.2±88.2	11.376	< 0.001*
Serum Iron	Range	155 – 543	66 – 176		
(µg/dl)	Mean±SD	315.5±117.2	119.3±32.4	8.839	< 0.001*
Total iron binding	Range	122 – 333	250 – 345		
capacity (µg/dl)	Mean±SD	207.4± 49.2	281.8± 19.7	-7.692	< 0.001*

MCV= mean corpuscular volume, MCH= mean corpuscular hemoglobin MCHC= mean corpuscular hemoglobin concentration. WBCs= White blood cells

4. DISCUSSION

MRI is a crucial instrument in the current management of thalassemia patients owing to its ability to measure iron overload in various organs non-invasively and without contrast [19].

The aim of this work was to evaluate pituitary iron overload in children with β thalassemia

using MRI T2* and correlate MRI T2* and biochemical markers of iron overload with pituitary hormones.

In the current study, significantly lower anthropometric measurements including weight, Z score of weight, height, Z score of height and body mass index (BMI) were found in patients compared with control group.

This comes in agreement with Al-Naama et al. [20] and Alsharnoubi et al. [1], they found significantly lower BMI, BMI Z-score, height, and weight in patients of both sexes with β-TM than in controls. Short stature was observed in 52% of patients with β –TM and as regard to BMI, our results are in agreement with Eissa and El-Gamal [21] and Hagag et al. [19] who found significantly lower BMI in patients compared with controls which was explained by chronic nature of the disease.

Growth retardation in thalassemic children could be attributed to chronic anemia caused by inadequate transfusion, hypoxia, and other endocrine disorders which occur due to iron overload causing failure of puberty and consequent growth retardation [22].

In the current study, there was delayed puberty according to tanner staging in patients with thalassemia compared with control group.

This is in agreement with Al-Naama et al. [20] who reported that 63% of male patients with beta thalassemia major ≥ 14 years of age and 54.5% of female patients with beta thalassemia major ≥ 13 years of age showed signs of delayed puberty. In contrast, all individuals in the control group exhibited normal pubertal development and Dhouib et al. [23] who reported that 42% of studied patients had a delayed puberty.

There was significantly higher prevalence of amenorrhea in female patients with thalassemia compared to control group. Also Sutay et al. [24] studied 56 females with βTM and 50 healthy girls. The cases and controls were further divided into 2 groups based on age from 8-12 years and > 12 up to 16 years. They found no cases and 26.3% of controls had attained menarche in the age group of 8-12 years whereas 11.4% of cases and 93.3% of controls in the age group of >12 years had attained menarche.

Table 4. Comprison between patients and controls as regard thyroid hormones, basal GH, provocative GH, FSH, LH , bone age and Pituitary MRI T2*

Measure		Patients (n=30)	Controls (n=30)	t or X2	P value
TSH (IU/mL)	Range	0.7 - 5	1.8 – 5		
	Mean±SD	2.9 ± 1.7	2.9 ± 0.8	-0.211	0.833
Free T3 (pg/ml)	Range	2.7 - 6	1.0 – 4		
	Mean±SD	3.8 ± 1	3.5 ± 0.8	1.551	0.126
Free T4 (ng/dl)	Range	12 – 21.3	11 -20		
	Mean±SD	16 ± 2.3	15.2± 2.5	1.333	0.188
Basal GH	Range	0.2 – 4	7- 13		
	Mean±SD	1.2± 1	8.7± 1.4	-16.078	0.001*
GH after 30 minute	Range	0.2 – 11.9	6 – 12		0.001*
	Mean±SD	4.0 ± 2.8	8.2 ± 1.3	-3.917	
GH after 60 minutes	Range	0.9 – 10	4.0 – 3.4		
	Mean±SD	4.0 ± 2.8	7.9 ± 1.3	-2.409	0.001*
GH after 90 minutes	Range	0.4 – 8.6	7.0 – 13		
	Mean±SD	2.5± 2.3	8.8± 1.3	-13.229	0.001*
GH after 120	Range	0.2 – 4.3	6 – 12		
minutes	Mean±SD	1.4± 1	8.1± 1.3	-22.109	0.001*
	Range	0.1 – 3.8	2.5- 11.5		
FSH (mIU/ml)	Mean±SD	1.44± 1.15	5.72± 2.349	-11.67	<0.001*
LH (mIU/ml)	Range	0.1 – 5.2	2.5 – 12.5		
	Mean±SD	1.286±1.319	6.470±2.55	-12.74	<0.001*
	Range	10 -14	10 -18		
Bone age	Mean±SD	11.5± 1.4	12.8±2.5	-2.409	0.001*
Pituitary T2*	Range	5.83-16.34	10.24-54.37		
ms	Mean±SD	6.5 ± 29.9	40.0± 75.0	-17.681	0.001*

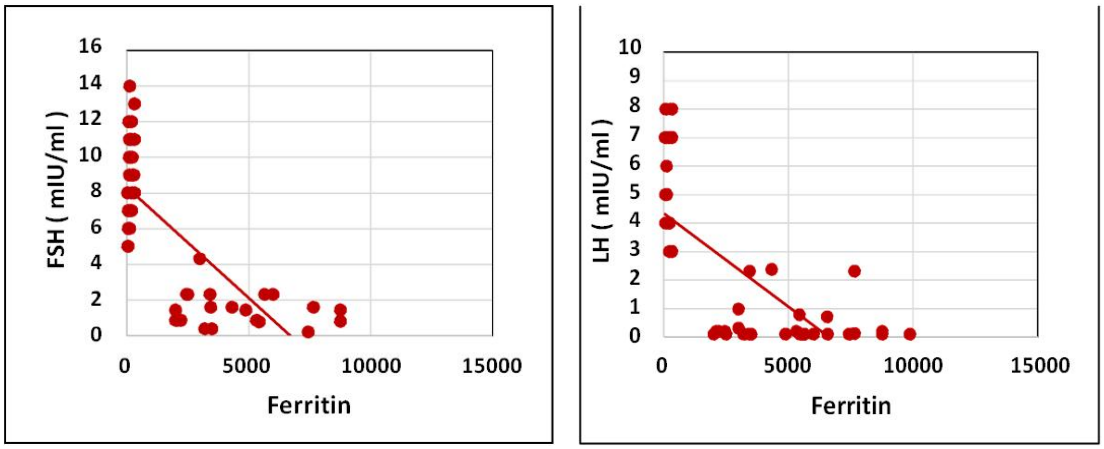

Fig. 1. Correlation between serum ferritin and FSH (Lt) and LH (Rt) in studied patients

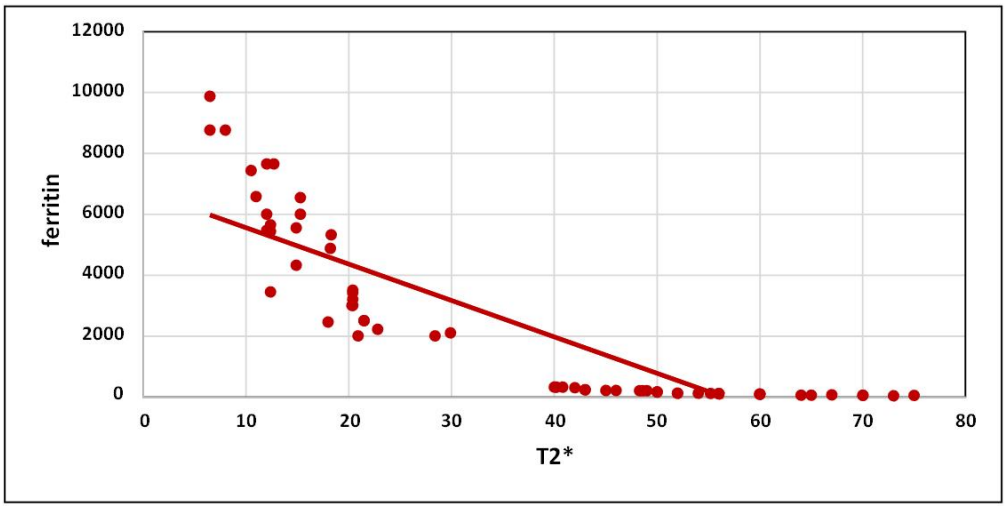

Fig. 2. Correlation between pituitary T2* and serum ferritin in studied patients

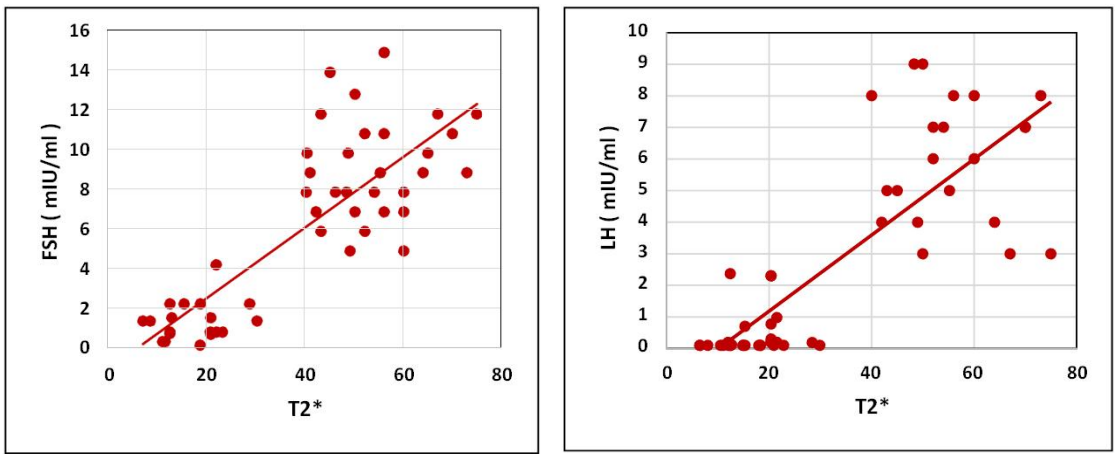

Fig. 3. Correlation between pituitary T2* and FSH (Lt) and LH (Rt) in studied patients

Table 5. Correlations between serum ferritin, pituitary T2* and anthropometric measurements and pituitary hormones of studied patients

Correlations				
	Serum ferritin (ng/ml)		Pituitary T2*(ms)	
	r	P-value	r	p-value
Wt (kg)	-0.620	0.001*	0.732	0.001*
HT (cm)	-0.659	0.001*	0.776	0.001*
BMI (Kg/m2)	-0.609	0.001*	0.556	0.001*
FSH (mIU/ml)	-0.772	0.001*	0.792	0.001*
LH (mIU/ml)	-0.383	0.003*	0.453	0.007
Pituitary T2* (ms)	0.401	0.001*		
Serum ferritin (ng/ml)	-------	------	- 0.866	0.001*
Basal GH (ng/ml)	- 0.774		0.871	0.001*
After 30 min	-0.562		0.453	0.001*
After 60 min	-0.612		0.596	0.001*
After 90 min	-0.678		0.798	0.001*
After 120 min	-0.743	0.001*	0.835	0.001*

Table 6. ROC curve of Pituitary T2* for detection of growth hormone , FSH, LH abnormality and comparison between pituitary T2* and serum ferritin as diagnostic tool for hormonal abnormality

ROC curve		Cutoff	AUC	P	sensitivity	specificity
Pituitary T2*	GH	20.0	0.855	<0.001	80%	70%
	LH	35.0	0.958	<0.001	100%	83.3%
	FSH	35.5	1.000	<0.001	100%	100%
Serum ferritin	GH LH	-	-	-	68.2%	100%
	FSH	-	-	-	100%	83.3%
		-	-	-	100%	100%

Hypogonadotropic hypogonadism is the most frequent endocrinopathy in patients with transfusion-dependent thalassemia affecting 70-80% of all thalassemia patients [25]. This complication is largely explained by toxic effect of iron overload secondary to chronic blood transfusions because the human body lacks a mechanism to excrete excess iron [26].

In our study, there were significantly higher serum ferritin and serum iron and significantly lower serum total iron binding capacity in studied patients compared with controls which could be explained by frequent packed RBCs transfusion and irregular iron chelators intake which was found in most of studied patients .

This comes in agreement with Eissa and El-Gamal [21] and Hagag et al. [19] who found the same results .

Iron overload in beta thalassemia could be explained by two main mechanisms, increased iron absorption due to ineffective erythropoiesis and repeated blood transfusion [19].

In the current study no significant differences were found between patients and control group as regard TSH, free T3 and free T4.

This is in agreement with Al-Hakeim et al. [27] who found no significant differences between thalassemic patients and healthy control as regard free T3, free T4, and TSH.

Sharma et al. [28] found hypothyroidism in only 4.7 % of patients with thalassemia.

The thyroid pituitary axis seems to be less sensitive to iron deposition damage than gonadal and GH axis. Hence, secondary hypothyroidism is rare in patients with thalassemia, which was not observed in our study.

In contrast to our study Drema et al. [29] found subclinical hypothyroidism in 24% of patients and in 2% overt hypothyroidism and explained the high prevalence of hypothyroidism in Indian patients with thalassemia by suboptimal chelation due to high cost of iron chelation therapy and poor compliance.

Thyroid dysfunction in thalassemia (primary hypothyroidism) is mostly due to iron deposition in the thyroids with varying frequency depending on the region, quality of management and treatment protocols [29].

In the current study there were significantly lower levels of FSH and LH in patients compared to control group.

Our results come in agreement with Sutay et al. [24] who found the same results.

Iron deposition may begin in the anterior pituitary gland in the first decade of life, but clinical symptoms are usually not apparent before puberty. Only reduced gonadotropin reserve was observed at the earlier stage, with intact gonadotropin pulse. Until hypogonadism occurs an asymptomatic process of pituitary siderosis may occur [4].

Hypogonadotropic hypogonadism is not only due to iron toxicity on gonadotropic cells, but also adipose tissue and leptin affection resulting in decreasing leptin synthesis and impairement of its role in sexual maturation and fertility as level of leptin increases dramatically in early puberty and has positive effect on hypothalamic pituitary-gonadal axis [6].

In contrast to our results Siripunthana et al. [30] found that the basal levels of serum LH and FSH were not significantly different between pubertal patients and controls suggesting that the hypothalamic– pituitary–gonadal axis is intact. They attributed their results to adequate treatment with blood transfusion at an appropriate time, effective iron chelation and relatively younger patients in their study.

In the current study there was significantly lower bone age in patients compared to control group. This is in agreement with Shah et al. [31] who found bone age deficit in 86% of patients with thalassemia Dhouib et al. [23] who reported that bone age delay was over one year in all patients with thalassemia and Imtiaz et al. [32] who found significant lower bone age in patients with thalassemia compared with control group.

In the present study there was significantly lower serum growth hormone level in patients compared to control group .This is in agreement with Azeez et al. [33] who found significant decrease in serum GH in male patients with thalassemia compared with that of control group and Imtiaz et al. [32] found significantly lower mean growth hormone level among children with thalassemia compared with control group.

Moreover, Ziari and Rahmani [34] found that 54.74% of patients with thalassemia major had growth hormone secretion disorder and Dhouib et al. [23] found GH deficiency in 35% of studied patients.

In contrast to our study Dhale et al. [35] found that the mean level of Growth Hormone among thalassemia major patients was in the normal range and insignificantly different from their controls.This could be explained by regular blood transfusion, effective chelation therapy and aggressive nutritional supplements.

In the current study, there is statistically significantly lower level of pituitary T2* in patients compared to control group.

This comes in agreement with Çetinçakmak etal. [36], Bozdag et al. [37] and Karadag et al. [16] who found the same results .

In the current study, there is a statistically significant negative strong correlation between ferritin with weight, height, BMI, Z score of height and Z score of weight and bone age in studied groups .

This comes in accordance with Moiz et al. [38] who found significant negative correlation between height for age z-score and serum ferritin levels and Rathaur et al. [39] who found (65.71%) of studied patients had short stature, 77% were underweight and rest had normal BMI and they found also statistically significant negative correlation between serum ferritin and short stature .

In the present study, there was a statistically significant negative correlation between serum ferritin with FSH and LH.

This comes in agreement with Hagag et al. [6], AL TN and Zuhairy [40] who found significant negative correlations between serum ferritin , FSH and LH. This could be explained by progressive damage of pituitary gland with subsequent decrease of gonadal hormones with progressive increase in iron load.

However Abo-Elwafa et al. [41] found insignificant correlation between serum ferritin and FSH, LH, estradiol and testosterone which

could be explained as there are other etiological factors responsible for hypogonadism in these patients, the most important one is chronic persistent anemia, hepatic affection and synchronous association of other endocrine dysfunction as hypothyroidism.

In the current study, there was statistically significant negative correlation between serum ferritin with basal GH and provocative Growth hormone level after 30 minutes, after 60 minutes, after 90 minutes, and after 120 minutes.

This is in agreement with Azeez et al. [33], Fadlyana et al. [42] and Jahargirdar et al. [43] who found significant negative correlation between serum ferritin level and Growth hormone.
In this study, there was statistically significant positive correlation between pituitary T2* with weight, height, BMI, Z score of height and Z score of weight, while no statistically significant correlation was present with bone age .

This could be explained by Moiz et al. [38] who found that growth failure in thalassemia major is multifactorial, iron overload is one of the main factors, frequent blood transfusions can control pretransfusion hemoglobin levels, but if serum ferritin levels are greater than the desired levels, patients'physical growth can be affected.

In the present study, there was a statistically significant negative correlation between pituitary T2* with serum ferritin.

This is in agreement with Bozdag et al. [37] who found significantly higher pituitary iron accumulation in β -TM with hypogonadism than both healthy subjects and β -TM patients without hypogonadism and Karadag et al. [16] who found negative correlation between serum ferritin level and pituitary T2* value in patient with hypogonadism .

In contrast to our results, Çetinçakmak et al. [36] found positive correlation between Pituitary T2* values and serum ferritin.

In the present study, there was statistically significant positive correlation between pituitary T2* with FSH and LH.

This comes in agreement with Moiz et al. [38] who reported that Pituitary MRI studies demonstrated that severe pituitary iron accumulation may develop around 4 years of age, pubertal delay is apparent 10 years later when tissue changes often become irreversible. Beside iron-induced damage and chronic hypoxia (low pre- transfusion hemoglobin) other factors contributing to final adult height include ethnicity, genetic composition, hormonal status, nutritional deficiencies, degree of chelating agents utilization, emotional factors, endocrinopathies and chronic liver disease.

In this study, the Receiver Operating Characteristics (ROC) analysis was performed to examine the ability of pituitary T2* for predicting GH, LH and FSH abnormality.

The pituitary T2* carried the sensitivity of 80%,100% and 100% and specificity of 70%,83.3% and 100% for predicting GH hormone abnormality, LH and FSH respecetively.

This comes in agreement with Mousa et al. [44] who reported that pituitary T2* had sensitivity and specificity of 100% and 88%, respectively in patient with short stature and hypogonadism.

5. CONCLUSION

There was a significant negative correlation between Pituitary T2* and serum ferritin. There were a significant positive correlations between pituitary MRI T2*and anthropometric measurement and pituitary hormones of studied patients.

Pituitary iron overload can be detected by MRI T2* which is a diagnostic tool in detecting pituitary iron overload with subsequent effect on hormonal secretion
especially growth hormone.

6. RECOMMENDATIONS

Children with thalassemia should undergo meticulous follow up regarding regular blood transfusion, regular iron chelators in a proper manner and doses and routine use
of MRI T2* in the evaluation of pituitary iron overload before irreversible damage occur in the pituitary gland.

CONSENT AND ETHICAL APPROVAL

This case control study was carried out after approval from ethical committee of research center of Tanta University permission number 32211/03/18 and obtaining written consents from

the parents of all children included in this study and was conducted on 30 children with transfusion dependent β-thalassemia major including 19 females and 11 males with their age ranging from 10 - 18 years and mean age value of 12.8 ± 2.4 who attended to Hematology Unit, Pediatric Department, Tanta University Hospital in the period from September 2018 to September 2019 and 30 healthy children of matched age and sex as a control group

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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