Study of Thyroid gland function and serum circulating ferritin in Beta- thalassemia Major female patients in Tikrit city

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Abstract

Beta-thalassemia probably is the most common single gene disorder causing a major genetic health problem in the world. People of Mediterranean, Middle Eastern, African, and Southeast Asian descent are at higher risk of carrying the genes for thalassaemia. Endocrine complications in Thalassaemia Major Patients with multi-transfused Thalassaemia Major develop severe endocrine complications. The aim of the study is to determine the relation between serum circulating ferritin and thyroid gland function in Thalassemic patients. Patients & methods:- A cross sectional study was conducted on β-thalassaemia major patients whom attended the thalassaemia center in Tikrit Teaching Hospital (TTH) from beginning of January to the mid of June 2014. Fifty six β- thalassemia major female patients aged 10 to 16 were participated in the study. Thirty nine female subjects apparently healthy, with no family history of hereditary blood disease attendants to out-patient pediatric clinic, who were assessed by a pediatrician, all control healthy subjects aged 10 to 16 years. Body weight & height and serum ferritin, serum TSH, T3, & T4 were measured. Results:- There was a highly significant increase in serum circulating ferritin concentration in female thalassemic patients as compare with control subjects. Also, there is significant increase in serum Thyroid stimulating hormone (TSH) concentration in female thalassemic patients. However, there is significant reduction in serum T3 and T4 concentrations in female thalassemic patients as compare with female control subjects. Conclusion; Thalassemic female patients had a lower T3 & T4 as compare with normal healthy female control subjects of same age.

Key words:- Body weight, serum ferritin, T3, T4, & TSH, and Thalassemic female patients

Introduction

Thalassemia has been classified by the world health organization as a major public health problem (1). It occurs throughout the world and regarded as one of the major health problems in endemic regions as the, Middle East, North Africa, Mediterranean countries and Asia, (2,3). Beta-thalassemia probably is the most common single gene disorder causing a major genetic health problem for

hemoglobinopathies throughout the world (4,5).

The clinical manifestations are seen within the first three to six months after birth and are characterized by severe anemia because the decreasing levels of fetal hemoglobin (HbF) cannot be replaced by normal adult hemoglobin, (6).

Endocrine complications in Thalassaemia Major Patients with multi-transfused Thalassaemia Major develop severe endocrine complications. Iron overload due to multiple transfusions is the main cause of such complications. Iron accumulates in many tissues such as liver, heart and endocrine glands (7,8).

Thyroid gland produce two distinct hormones, triiodothyronine (T3) and thyroxin (T4). These hormones are responsible for raising the level of activity in the systems essential for exercise performance, (9,10,11).

Iron overload is a consequence of frequent blood transfusion, which is the most important treatment modality for thalassaemia major (12).

The aim of the study is to determine the relation between iron overload and thyroid function in Thalassemic patients.

Patients & Methods

A cross sectional study was conducted on β-thalassaemia major patients whom attended the thalassaemia center in Tikrit Teaching Hospital (TTH) in Tikrit from March 2014 to the mid of June 2014. Fifty six β- thalassemia major female patients aged 10 to 16 were participated in the study. Thirty nine female subjects apparently healthy, with no family history of hereditary blood disease attendants to out-patient pediatric clinic, who were assessed by a pediatrician, all control healthy subjects aged 10 to 16 years.

Body weight was measured to the nearest 100 gram & body height was measured to the nearest centimeter (CM).

The circulating ferritin concentrations in the serum of all subjects included in this study were determined quantitatively by a microplate immunoenzymometric assay by using a kit supplied from

(Monobind, USA) and measured by ELISA (9).

Thyroid stimulating hormone (TSH), T3 & T4 for Females were measured, (10-11).

Results

There is a high significant decrease in body weight & height of female thalassemic patients as compare with female counterpart of control subjects of same age.

Moreover, there is a high significant decrease in body mass index (P≤0.01) in female patients (18.825 ± 2.8 kg/m2) as compare with BMI of female control subjects (23.61 ± 3.6 kg/m2), as shown in (table -1).

Also, there is significant increase in serum Thyroid stimulating hormone (TSH) concentration (P≤0.01) in female thalassemic patients (4.412 ± 0.21 µIU/ml) as compare with female control subjects (3.22 ± 1.23).

However, there is highly significant reduction in serum T4 concentration (P≤0.01) in female thalassemic patients (0.533 ± 0.225 µg/dl) as compare with female control subjects (6.667 ± 0.71 µg/dl).

Furthermore, there is significant reduction in serum T3 concentration in female thalassemic patients (1.034 ± 0.381 ng/ml) as compare with female control subjects (1.195 ± 0.29 ng/ml).

Table (3) Show the mean & standard deviation of packed cell volume & hemoglobin, white blood count, serum ferritin between female patients and female controls:

Regarding packed cell volume (PCV): there is a high significant reduction (p≤0.01) in female thalassemic patients (27.93 ± 1.23 L/L) as compare with female control subjects (38.83 ± 2.03 L/L).

Moreover, regarding hemoglobin (Hb): there is a highly significant reduction (p≤0.01) in Hb of female thalassemic patients (8.27 ± 0.41 gm/dl) as compare with female control subjects (13.72 ± 0.68 gm/dl).

Also, there is a highly significant increase in white blood cell count (9753 ± 734 cell/cm3) as compare with normal healthy control female subjects of same age (5841 ± 982 cell/cm3).

Moreover, there is a high significant increase (p≤ 0.01) in serum ferritin

in female thalassemic patients (3513.65 ± 1412.2 ng/ml) as compare with female controls of same age (53.54 ± 7.93 ng/ml), Table 3.

Discussion

In the present study, there is highly significant reduction in serum T4 concentration in female thalassemic patients as compare with female control subjects. Furthermore, there is significant reduction in serum T3 concentration in female thalassemic patientsas compare with female control subjects. Also, there is significant increase in serum Thyroid stimulating hormone concentration in female thalassemic patients as compare with female control subjects.

The abnormal thyroid function found in the presented patients was the isolated elevation of TSH, which was consistent with the diagnosis of compensated hypothyroidism, the most common thyroid dysfunction in all previous reports, (12-13).

Thyroid dysfunction in β-thalassemic patients has been reported in various prevalence, ranging from a low prevalence of 0-12% (14).

Previous study have stated that impaired thyroid function is present in a considerable proportion of transfusion-dependent beta-thalassemia patients with associated iron overload, (15).

Impaired thyroid function is frequent among present thalassaemia major patients and this necessitates regular follow up and early commencement of chelation therapy to prevent such complication, (17).

Previous study was done in Irbil –Iraq, it was found that the mean levels of thyroid hormones; T3 and T4 were significantly lower ($P<0.001$) among thalassaemia patients, while the mean TSH level was higher ($P \leq 0.003$) compared to the control group, (18). Also, in the same study, nineteen patients (24.3%) had hypothyroidism, of these, 2 patients (2.5%) had overt hypothyroidism (low T4, and high TSH) and 17 patients (21.8%) had subclinical hypothyroidism (normal T4 and high TSH). They were heavily iron overloaded (mean S. Ferritin = 5250 ng/ml).

The incidence of overt and subclinical hypothyroidism in b-

thalassemia was reported to be relatively high especially in patients with long standing B-thalassemia, (19).

In the present study, there is a significant reduction in PCV and hemoglobin (Hb) of female thalassemic patients as compare with female control subjects.

Other factors like hypoxia due to persistent anemia and perfusion defect, also contribute to the derangement. Hypothalamic pituitary axis, thyroid, para-thyroid, adrenal, pancreas, gonads, all show hypoactivity, (16).

Previous study found that the mean T4 of cases (7.36 ± 1.61 μg/dL) was significantly lower ($p<0.001$) than that of controls (9.30 ± 2.15 μg/dL). The mean TSH level was significantly higher ($p<0.01$) in cases (3.56 ± 1.49 μg/dL) as compared to controls (2.31 ± 2.74 μg/dL), (20).

In the present study, there is a high significant increase in serum ferritin in female thalassemic patients (3513.65 ± 1412.2 ng/ml) as compare with female controls of same age (53.54 ± 7.93 ng/ml).

Iron overload causes deposition of iron in the thyroid gland, with consequent fibrosis of the glandular parenchyma, and progressive thyroid dysfunction going through different degrees of severity up to overt hypothyroidism (21).

Thyroid dysfunction is known to occur frequently in thalassaemia major, but its prevalence and severity varies in different cohorts, and long-term natural history is poorly understood, (20-22).

The thyroid gland appears to fail before the thyroid-pituitary axis, which is less sensitive than the gonadal axis to iron-induced damage, (21-22).

In the present study, there is a highly significant increase in white blood cell count (9753 ± 734 cell/cm3) as compare with normal healthy control female subjects of same age (5841 ± 982 cell/cm3).

A high increase in white blood cells and associated with a high concentrations of plasma ferritin and labile cell iron which are considered responsible in the formation of free radicals and the production of reactive oxygen species (ROS) may lead to cell and organ damage (23-24).

From the present result & previous findings, these findings reinforce the importance of the regular follow up of patients with b-thalassaemia major and thalassaemia intermedia for early detection and management of associated complications. In this way, the future prevalence of endocrine abnormalities can be lessened, (19-20).

High prevalence of hypothyroidism among thalassemic patients signifies the importance of regular screening for evaluation of endocrine function in these patients; especially when short stature is present, (25, 27).

However, as a result of hyper transfusion therapy and increased longevity, iron tissue toxicity has become more common, and contributes significantly to morbidity in these patients due to damage of several organs & endocrine glands by Iron overload, (28).

The present study concluded the followings;-

Thalassemic female patients had a higher significant increase in serum Thyroid stimulating hormone (TSH) concentration as compare with female control subjects. However, female thalasssemic patients had a lower T3 & T4 as compare with normal healthy female control subjects of same age.

The present study recommends the followings;

1-Assessment of pituitary hormone especially growth hormone by carry out hormonal test for both genders as a routine follow up of thalassaemic patients.

2- Assessment of certain hormones concentration is necessary for the follow up of the thalassemic patients especially during puberty.

References

1. Guyton and Hall Text book of medical physiology, 11th edition Philadelphia, Pennsylvania, 2010.

2. Muncie HL, Campbell JS. Alpha and beta thalassaemia. Am. Family Physician. 2009; 80(4): 339-44.

3. Barrett, KE., Barman, SM., Scott Boitano, Brooks, HL. Ganong′s Review of medical physiology, 23rd ed. McGraw Hill company, 2010.

4. Thein SL. Genetic insights in to the clinical diversity of beta

thalassemia. Br J Haematol. 2004; 124: 264-74.

5. Mohaisen H Adaay, Moayed M Al-Anzy, Abdul-Monaim H Al-Samarrai, Khudair A Al-Tikriti, Firas A Al-Samarrai. Some Observations on the Occurrence of β-Thalassemia in Mosul. Iraqi J. Med. Sci. 2011; 9 (3): 270-274.

6. Dammas AS, Adedoyin MA, Cheriya A. Experience with thalassemia major in Al-Baha. Ann Saudi Med J 1995; 15 (6): 589-593.

7. Modell B, Khan M, Darlison M. Survival in beta-thalassemia major in the UK: data from the UK Thalassemia Register. Lancet. 2000; 355(9220): 2051-2052.

8. Mohanty D, Colah RB, Gorakshakar AC, Patel RZ, Master DC, Mahanta J, et al. Prevalence of beta-thalassemia and other haemoglobinopathies in six cities in India: a multicentre study. J Community Genet. 2013 Jan; 4(1):33-42.

9. Steiene-Martin EA, Lotspeich-Steininger CA, Koepke JA. Clinical Hematology: Principles, procedures, correlations. 2nd ed. Philadelphia: Lippinscott-Raven; 1997.

10. Rund D, Rachmilewitz EA. Beta-thalassaemia. New Engl J Med 2005; 353: 1135-46.

11. Vaananen I., Vasankari T., Manty Saari M., and Vinko V. Hormonal responses to daily strenuous walking during 4 successive days. Eur. J. Appl.Physiol. 2002; 88: 122-127.

12. Cunningham MJ, Macklin EA, Neufeld EJ, Cohen AR. Complications of beta-thalassemia major in North America. Blood. 2004 Jul 1; 104(1): 34-9.

13. Tiosano D, Hochberg Z. Endocrine complications of thalassemia. J Endocrinol Invest 2001; 24: 716-23.

14. Somchit Jaruratanasirikul, Malai Wongcharnchailert, Vichai Laosombat, Pasuree Sangsupavanich, Kalaya Leetanaporn. Thyroid Function in β-Thalassemic Children Receiving Hypertransfusions with Suboptimal Iron-Chelating Therapy. J Med Assoc Thai 2007; 90 (9): 1798-802.

15. Al-Hader A, Bashir N, Hasan Z, Khatib S. Thyroid function in children with beta-thalassemia

major in north Jordan. J Trop Pediatr. 1993; 39: 107–10.

16. Sabato AR, de S V, Atti G, Capra L, Bagni B, Vullo C. Primary hypothyroidism and the low T3 syndrome in thalassaemia major. Arch Dis Child 1983; 58: 120-7.

17. Mehrvar A , Azarkeivan A , Saberi Nejad, Mehrvar N, Faranoosh M, Vosoogh P. Prevalence of hypothyroidism and hypoparathyroidism in Iran. Blood J. 2008 ; 5(1):53-59.

18. Khider, Noori A., Fayzeh Mohamed Hussein. Assessment of thyroid function among transfusion dependant Thalassaemics in Erbil. Middle East Journal of Family Medicine. 2014; 12(1): 5-13.

19. Filosa A, Di Maio S, Aloj G, Acampora C. Longitudinal study on thyroid function in patients with thalassemia major. J Paediatr Endocrinol Metab. 2006; 19: 1397-404.

20. Aydinok Y, Darcan S, Polat A, et al. Endocrine complications in patients with beta-thalassemia major. J Trop Pediatr. 2002;48(1):50–4.

21. De Sanctis V, De Sanctis E, Ricchieri P et al. Mild Subclinical hypothyroidism in thalassemia major: prevalence, multigated radionuclide test, clinical and laboratory long-term follow-up study. Pediatr Endocrinol Rev 2008; 6: 174–180.

22. Taysir S. Garadah, Najat A. Mahdi, Ahmed M. Jaradat, Zuheir A. Hasan and Das S. Nagalla. Thyroid Function Status and Echocardiographic Abnormalities in Patients with Beta Thalassemia Major in Bahrain. Clinical Medicine Insights: Cardiology 2013:7: 21-27

23. Gamberini MR, De Sanctis V, Gilli G. Hypogonadism, diabetes mellitus, hypothyroidism, hypoparathyroidism: incidence and prevalence related to iron overload and chelation therapy in patients with thalassaemia major followed from 1980 to 2007 in the Ferrara Centre, Pediatr Endocrinol Rev. 2008; 6 Suppl 1: 158-69.

24. Gharib, H., Tuttle, R.M., Baskin, H.J., Fish, L.H., Singer, P.A., McDermott, M.T. Consensus statement: subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American

Thyroid Association, and The Endocrine Society. Thyroid. 2005;15: 24–28.

25. Gathwala G, Das K, Agrawal N. Thyroid hormone profile in Beta thalassemia major children .Indian J Pediatr. 2009; 4(2): 20-9.

26. Sharma S and Aggarwal R. Evaluation of thyroid hormones in Beta-thalassemic children of north india. UJMDS. 2014; 2 (1):39-42.

27. Eshragi P., Tamaddoni, A., Zarifi, K., Mohammadhasni, A. Thyroid function in major thalassemia patients: Is it related to height and chelation therapy?. Caspian J Intern Med. 2011; 2(1): 189-193.

28. Mula-Abed WA, Al Hashmi H, Al Muslahi M, Al Muslahi H, Al Lamki M. Prevalence of Endocrinopathies in Patients with Beta-Thalassaemia Major. Intern J Endocr. Met Group. 2008; 6 (2): 23(4):257- 62.

Table 1 The mean & standard deviation (SD) of age, body weight, height & BMI.

Parameters	**Control (39)**	**Patients (56)**	**P value**
Age (years)	13.91 ± 1.01	14.54 ± 1.58	NS
Body weight (Kg)	51.42 ± 8.12	34.32 ± 6.21	0.001
Height (Cm)	147.14 ± 8.4	135.53 ± 6.9	0.001
BMI (kg/m^2)	23.61 ± 3.6	18.825 ± 2.8	0.01

Table 2 Show the mean & standard deviation (SD) of serum TSH, T3 & T4 in female patients and control subjects.

Parameters	**Control**	**Patients**	**P value**
TSH **(µIU/ml)**	3.22 ± 1.23	4.412 ± 0.21	0.05
T3 (**ng/ml)**	1.195 ± 0.29	1.034 ± 0.381	0.05
T4 **(µg/dl)**	6.667 ± 0.71	0.533 ± 0.225	0.001

Table 3-The mean & standard deviation (SD) of PCV, hemoglobin, & white blood cells.

Parameters	**Control (39)**	**Patients (56)**	**P value**
PCV (L/L)	38.83 ± 2.03	27.93 ± 1.23	0.01
Hemoglobin (gm/dl)	13.72 ± 0.68	8.27 ± 0.41	0.01
WBCs ($Cell/Cm^3$)	5841 ± 982	9753 ± 734	0.01
Ferritin (ng/ml)	53.54 ± 7.93	3513.6 ± 1412.2	0.01