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Endocrine Disorders in Beta- thalassemia Major Patients

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Abstract

Background

Thalassemia is the most common hereditary disorder worldwide. The patient's' survival is dependent on lifetime blood transfusion which leads to iron overload and its toxicity on various organs including endocrine glands. The study aimed to investigate endocrine disorders in patients with Beta-thalassemia major in the Southern Khorasan province, Iran.

Materials and Methods

In this descriptive cross sectional study of the 42 patients with beta- thalassemia major blood samples were taken in the fasting to check laboratory tests such as fasting blood sugar, calcium, phosphorous, thyroid stimulating hormone (TSH), thyroxine (T4), luteinizing hormone (LH), follicle stimulating hormone (FSH), parathyroid hormone (PTH), Ferritin. Data analyzed using SPSS version 16.0 software.

Results

Results showed that 85.7% of patients had endocrine disorders. The most common endocrine abnormalities were hypogonadism (71.4%), hypoparathyroidism (21.4%), diabetes (14.3%), and hypothyroidism (7.2%), respectively.

Conclusion

Our results concluded that endocrine evaluation must be carried out regularly in patients with beta-thalassemia major. Patients who have abnormal endocrine laboratory results should be reevaluated for compliance with chelation therapy and the transfusion program.

Key Words: Children, Beta-thalassemia Major, Diabetes Mellitus, Endocrine Disorders.

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1- INTRODUCTION

Endocrine disorders are disorders of the endocrine glands such as hypogonadism, insulin-dependent diabetes, hypothyroidism and hypoparathyroidism which can be seen in some hereditary hemolytic diseases secondary to treatment (1-4). Haemoglobinopathies (thalassemia and sickle cell anemia) are the most common inherited genetic disorders all over the world. Annually, 240,000 neonates with major haemoglobinopathies, and at least 190 million carriers are born worldwide. Beta-thalassemia (β-thalassemias) is characterized by abnormalities in construction of the beta chain in hemoglobin and the prevalence of the disease is 1 per 100 thousand people in the world (5).

Thalassemia in Iran is unfortunate and approximately thirty thousand people are infected and Each year the numbers are added to this (6, 7). The survival of patients with beta- thalassemia major is dependent on the lifetime blood transfusion which leads to iron overload and its toxicity effects on various organs including the endocrine glands (8). Despite improvements in chelation therapy to reduce the iron overload in the recent years (9) which has improved the patients' life, endocrine disorders are still serious problems that threaten the quality of patients' life (10-15).

According to the development in the therapeutic interventions and increased longevity of patients, complications such as endocrine disorders, can be seen more frequently. As the complications treatment is both costly and time consuming, early diagnosis can reduce the mortality rate and help the patients to experience the more active life. Given that statistics which can be found in the textbooks related to developed countries, either genetic prevalence of the disease or careful monitoring of the therapeutic interventions in those countries differ from developing countries, and the existence of both racial differences and absence of documented reports associated with endocrine disorders, the study aimed to evaluate endocrine disorders in Beta-thalassemia major patients of the Southern Khorasan province, Iran.

2- MATERIALS AND METHODS

In this descriptive cross sectional study forty-two β-thalassemia major patients older than 10 years who had referred to Vali-Asr hospital clinic with official records, Birjand city, South East of Iran, selected through census method and evaluated from Jan 2015 to Dec 2015.

Blood samples were taken while the patients were fasting for 12 hours after explaining and obtaining written consent from patients and demographic data collection. The samples were taken with a syringe 20 ml and evacuated in the tube containing clot activator, held vertically until they clot. Then the samples were centrifuged within 15 minutes and some of the serum was removed and poured into 4 1.5 ml Microcentrifuge Tubes, USA. One vial used for laboratory tests such as fasting blood sugar, Calcium, Phosphorous by appropriate kits and biochemical devices in Vali-Asr hospital laboratory.

The remaining vials were kept in the freezer at a temperature of minus twenty degrees. At the time of experiment the 3 remaining vials was brought opened and mixed then other laboratory tests such as thyroid stimulating hormone (TSH), thyroxine (T4), luteinizing hormone (LH), follicular stimulating hormone (FSH), parathyroid hormone (PTH), estradiol and testosterone, and ferritin, were measured by VIDAS Kits using fluorescence method. Laboratory values are shown in **Table.1**. The " Prestige Auto Analyzer" and " Vidas" are widely known as valid tools for measuring biochemical laboratory and hormonal tests which are used daily in laboratory. Reliability of the " Prestige

Auto Analyzer" and " Vidas" was assessed through test-retest (double-check a blood sample) before study and their reliability coefficient was 0.98. In this study laboratory test results have been reported based on both a reference and the auto analyzer kit which was being used. Fasting plasma glucose equal or greater than 126 mg/dl were considered as diabetes (16). People aged 6 months to 15 years which TSH levels was more than 6.2 mcg/ml and adult with TSH serum levels more than 5.7 mcg/ml considered as hypothyroidism (17).

Thence patients with hypothyroidism divided into two groups, overt and subclinical. The patients with hypothyroidism with T4 levels lower than the normal range assigned as overt and those with normal T4 assigned as subclinical (17). The T4 level in the age group of 4 to 10 years less than 6.4 mcg/dl and in the age group of 10 to 15 years less than 5.5 mcg/dl was considered as lower than the normal range (17). This amount sets less than 5 mcg/dl in adults (17). Hypoparathyroidism was defined as calcium < 8.1mg/dl, phosphorous > 4.5 mg/dl and parathyroid hormone < 11pg/ml (17). Hypogonadism defined as luteinizing hormone <1.1 IU/L for men and luteinizing hormone <2.9 IU/L for women in follicular phase or less than 1.5 in luteal phase (17). Also, follicle stimulating hormone less than 1.1 IU/L in men and less than 1.5 IU/L for women in follicular phase or less than 0.2 in luteal phase included this definition (17).

This study conducted by the approval of University Ethics Committee which was gained by disclosing research methods and objectives and after obtaining written consent from all participants. Inclusion criteria were all β-thalassemia major patients older than 10 years who had referred to Vali-Asr hospital clinic with official records from Jan 2015 to Dec 2015. The patients who had verified endocrine disorder such as diabetes, thyroid dysfunction, parathyroid dysfunction or hypogonadism and were under treatment excluded from the study. The collected data analyzed by descriptive statistics and analytical tests using SPSS version 16.0 software. Data analysis was carried out with Independent t-test and Chi-square. P-value of less than 0.05 considered as significant.

Table-1: Laboratory Parameters of 42 Patients with Beta Thalassemia Major

Parameters	Mean± SD	Min	Max
FBS (mg/dl)	125 ± 89.4	69	418
LH (IU/L)	1.96 ± 5	0.1	28.4
FSH (IU/L)	2.01 ± 2.99	0.1	11.67
TSH (mcg/ml)	3.08 ± 3.07	0.87	20.2
T4 (mcg/dl)	5.82 ± 0.88	4.4	8.29
PTH (pg/ml)	22.99 ± 11.49	4	52
Ca (mg/dl)	8.74 ± 0.64	6.7	10.10
P (mg/dl)	88.8 ± 14.36	3.8	70
Ferritin (µg/l)	3759.5 ± 2531.75	37	9275

3- RESULTS

The mean age of participants was 14.38±6.63 years old (54.8 % male, 45.2% female). Mean and standard deviation of the serum LH and FSH levels in patients were 1.96±5 IU/L and 2.01±2.99 IU/L.

Also, 71.4% of patients with beta thalassemia major had hypogonadism and 28.6% of patients were not affected by the disorder. Mean and standard deviation of the serum PTH, Ca, phosphorous level in patients were 22.99±11.49 pg/ml,

8.74±0.64 mg/dl and 88.8±14.36 mg/dl, respectively. 21.4% of patients with beta thalassemia major had hypoparathyroidism and 78.6% of patients were not affected by the disorder. Mean and standard deviation of the serum fasting blood sugar (FBS) levels in patients were 124.19±89.42mg/dl. 14.3% of patients with beta thalassemia major had diabetes mellitus (FBS ≥ 126mg/dl), and in 85.7% of patients fasting blood glucose was less than 126mg/dl.

Mean and standard deviation of the serum TSH and T4 levels in patients were 3.08±3.07 mcg/ml and 5.82±0.88 mcg/dl, respectively; 7.2% of patients with beta thalassemia major had hypothyroidism and 92.8% of patients were not affected by the disorder. 33.3% of patients with hypothyroidism (2.4% of all the patients), were overt and 66.6% (4.8% of all the patients) were subclinical. Mean and standard deviation of the serum ferritin levels were 3759.5±2531.75 µg/L. Comparing the mean ferritin levels in β-thalassemia major patients with endocrine disorders and the others about none of the endocrine abnormalities was significant (P>0.05) (**Table.2**).

According to the study most of the patients with beta thalassemia major (40.5%), had at least one endocrine disorder (**Table.3**). Comparison the frequency of serum ferritin levels in patients with thalassemia major with endocrine disorders and the others without that about none of the endocrine abnormalities was significant (P>0.05)(**Table.4**).

Table-2: Comparing the Mean Serum Ferritin in Beta- Thalassemia Major Patients with or without Endocrine Disorders

Disorder	Group	Frequency (%)	Mean ± SD	Independent t-test
Diabetes	With disorder	6 (14.3)	4370.16±2871.90	T = 0.633
(µg/l)	Without disorder	36 (85.7)	3657.72±2501.14	P = 0.530
Hypothyroidism	With disorder	3 (7.2)	5147±2485.06	T = 0.985
(µg/l)	Without disorder	39 (92.8)	3652.76±2535.17	P = 0.331
Hypoparathyroidism,	With disorder	9 (21.4)	4632±3277.86	T = 1.172
(µg/l)	Without disorder	33 (78.6)	3521.54±2292.13	P = 0.248
Hypogonadism	With disorder	30 (71.4)	3991.83±2470.25	T = 0.939
(µg/l)	Without disorder	12 (28.6)	3178.66±2699.65	P = 0.353

Table-3: The Prevalence of Beta- Thalassemia Major with one or more Endocrine Disorder

Number of disorders	Frequency	Percent
No disorder	11	26.2
One	17	40.5
Two	11	26.2
Three	3	7.1
Total	42	100

Table- 4: Comparing the Frequency of Serum Ferritin level in Beta- Thalassemia Major Patients with or without Endocrine Disorders

Ferritin Level		<1000	1000-2000	>2000	Total	Chi square
	Groups	Frequency (%)	Frequency (%)	Frequency (%)	Frequency (%)	Test
Diabetes	with disorder	0 (0.0)	1 (16.7)	5 (83.3)	6 (100)	$Chi^2 = 0.972$ df = 2 P = 0.615
	without disorder	5 (13.9)	6 (16.7)	25 (69.4)	36 (100)	
Hypothyroidism	with disorder	0 (0)	0 (0)	3 (100)	3 (100)	$Chi^2 = 1.29$ df = 2 P = 0.524
	without disorder	5 (12.8)	7 (17.9)	27 (69.2)	39 (100)	
hypoparathyroidism	with disorder	1 (11.1)	1 (11.1)	7 (77.8)	9 (100)	$Chi^2 = 0.283$ df = 2 P = 0.868
	without disorder	4 (12.1)	6 (18.2)	23 (69.7)	33 (100)	
Hypogonadism	with disorder	2 (6.7)	5 (16.7)	23 (76.7)	30 (100)	$Chi^2 = 2.82$ df = 2 P = 0.244
	without disorder	3 (25)	2 (16.7)	7 (58.3)	12 (100)	
	Total	5 (11.9)	7 (16.7)	30 (71.4)	42 (100)	

4- DISCUSSION

The study assessed the endocrine disorders in patients with beta-thalassemia major in the Southern Khorasan province, South East of Iran. The results showed that most of the patients with beta-thalassemia major had endocrine disorders. Dramatic evolution in the three decades which has been made in the treatment of patients with β-thalassemia major, has led to increase the patients' lifespan. With regular blood transfusions, complications due to chronic anemia and bone changes are greatly relieved, but secondary diseases caused by the accumulation of iron in various tissues of the body arise that would be fatal if not treated (10-14). In this study the most common endocrine disorder was hypogonadism which was similar to the most studies done by other researchers in Iran such as, Shamshirsaz et al. (2003), Najafipour et al. (2008), Mostafavi et al. (2005), and Sayehmiri et al. (2016) (1, 12, 18, 19). The results of other studies, Chern et al. (2003), Gulati et al. (2000), and De Sanctis et.al (2004), are in line with the

present study (18, 20-22). Although, the incidence of hypogonadism has been decreased during the past two decades, it is still the most common endocrine disorder in patients with beta thalassemia major. The second endocrine disorder was hypoparathyroidism, there are many studies on the existence of hypoparathyroidism in patients with beta thalassemia major, as it is reported by Moaddab et al., Shamshirsaz et al. and Azami et al. (3, 18, 23), with different results which could be due to the differences in hypoparathyroidism definition, geographical area treatment and the vulnerability of patients.

The results of the study showed that 14.3% of patients with thalassemia major were diabetic. The results of Kashanchi et al. (2013), Moaddab et al. (2008), Najafipour et al (2008), Shamshirsaz et al. (2003), and Karamifar et al. (2003), are also shown the presence of diabetes in these patients as well (12, 18, 23-24). The results of the study showed the presence of hypothyroidism among patients with thalassemia major; 33.3% of patients with hypothyroidism (2.4% of all the patients), were overt and 66.6% (4.8% of all the patients), were subclinical.

The prevalence of clinical and subclinical hypothyroidism in patients with beta thalassemia major according to Kashanchi et al., is reported 19% and 1.65%, respectively (25). Other studies, Shamshirsaz et al. in Tehran (18), Moaddab et al. in Isfahan (23), Karamifar et al. in Shiraz (24), and Azami et al. in Iran (4), reported the results which are aligned with the present study. Since the serum ferritin level indicates the amount of iron overload during the last three months and given that prolonged contact with additional iron is needed to lead the endocrine disorders, may be an explanation for the lack of association between the ferritin level and endocrine disorders in the present study. Studies with larger sample size may show the connection. Also, using to the most reliable test for measuring the tissue concentration of iron (tissue hemosiderin) through biopsy, may be helpful for assessing a closer relationship between hemosiderosis and endocrine disorders (26).

4-1. Limitations of the study

Failure to achieve patients with pituitary gland disorders was one limitation of the study.

5- CONCLUSION

Our results concluded that endocrine evaluation must be carried out regularly in patients with beta thalassemia major. Patients who have abnormal endocrine laboratory results should be reevaluated for compliance with chelation therapy and the transfusion program. The authors suggest further studies in the field of mental health in order to increase the life expectancy of the patients and better contribution or adherence to the regular drugs regimen.

6- ABBREVIATION

- PTH: Parathyroid Hormone,
- FBS: Fasting Blood Sugar,
- Ca: Calcium,
- P: Phosphorous,
- TSH: Thyroid Stimulating Hormone,
- T4: Thyroxine,
- LH: Luteinizing Hormone,
- FSH: Follicle Stimulating Hormone.

7- CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

8- ACKNOWLEDGMENTS

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