Original Article ISSN (O):2395-2822; ISSN (P):2395-2814

Study of Thyroid Function Tests in Beta Thalessemia Major Patients in Children with Referance to Serum Ferritin Levels

Shruti Dhale[1], Rasika Hattewar[2], Shahaji Kure[2]

[1]Associate Professor, Department of Pediatrics, Grant Govt Medical College, Mumbai, India.

[2]Department of Pediatrics, Grant Govt Medical College, Mumbai, India.

Received: September 2020
Accepted: September 2020

ABSTRACT

Background: One of the most common endocrine problems in major beta-thalassemia is hypothyroidism (HT). The aim of this study was to evaluate thyroid function status in major β-thalassemia patients younger than 15 years old children. Due to repeated blood transfusions, there is iron deposition on thyroid gland.Decrease production of thyroid hormones according to body demand or defect in thyroid hormone receptors cause hypothyroidism. In several studies, hypothyroidism has been reported to be correlated with serum ferritin level,so serum ferritin levels were also measured; although in some studies there were no such correlations. Contrarily to significant iron deposition in thyroid gland, low activity remains about subclinical hypothyroidism. **Methods:** It is a prospective study and was conducted at St Georges Hospital, Mumbai, on diagnosed patients of thalassemia major admitted to the pediatric wards. Duration of the study was 3 months and 32 patients were included. Inclusion criteria: All admitted patients of thalasemia major aged 15 years and below. Exclusion criteria: 1) Very sick children, 2) Those suffering from malnutrition, 3) Chronic haemolytic anemia apart from thalassemia major, 4) Those who are already taking iron or thyroid medications, 5) Autoimmune thyroiditis was ruled out by antithyroid peroxidase and ant thyroglobulin antibody testing. Patients who were willing to participate and sign the informed consent were enrolled in the study. Thyroid function and ferritin assessment was done using ELISA kits. **Results:** The mean age of the studied thalassemia patients was 11.328 ± 2.408 years with no gender preponderance. Mean (SD) Sr. Ferritin levels was 3253.84 ±1142.67 ng/ml , mean (SD) free T3 level was 3.469 ±0.978pg/ml, mean (SD) free T4 levels was 1.658 ±1.142 pg/ml, mean (SD) TSH levels was 5.057 ±1.738 uIU/ml , and was not found to be statistically significant ($p > 0.001$). **Conclusion:** High prevalence of HT among thalassemic patients signifies the importance of regular screening for evaluation of endocrine function in these patients; especially when short stature is present.

Keywords: Beta thalassemia major, Hypothyroidism, Serum ferritin.

INTRODUCTION

The most common genetic disorder in the world is known to be thalassemia.[1] Beta thalassemia syndromes are disorders which are inherited and are characterized by deficiency in the production of beta globin chains resulting in ineffective erythropoiesis β-thalassemia major is a genetic disorder of beta globulin fiber gene. In β-thalassemic patients, β-globulin fibers are not enough (β^+) or do not exist (β^0). As a consequence of this, repeated blood transfusions are needed to maintain life, which in turn results in excessive iron being deposited in various organs resulting in early fatalities. In Beta Thalassemia Major patients the frequency of hypothyroidism ranges from 6 to 30 % among various countries depending on chelation strategies.[2] The quantity and duration of iron overload mainly determine the prognosis among such patients. Thyroid dysfunction mainly occurs by gland infiltration, chronic tissue hypoxia, free radical injury, and organ siderosis. The thyroid gland is affected much before the thyroid-pituitary axis, which is less susceptible than the gonadal axis to iron induced damage.[3] The combination of transfusion and chelation therapy has dramatically extended the life expectancy of thalassemic patients who can now survive into their fourth and fifth decades of life . However, frequent blood transfusion in turn can result in iron overload which may lead to various complications . Thalassemia's complications can be a result of many mechanisms. Most complications are caused by increased iron sedimentation in tissues like heart, endocrine glands and these results in heart failure, arrhythmia, hypothyroidism, diabetes mellitus and so on . The symptoms of hypothyroidism though non-specific can affect many organ systems, hence an annual laboratory evaluation of thyroid function is recommended in all beta thalassemics. Most of these complications occur slowly and appear in the second decade of a patient's life.

Decrease production of thyroid hormones according to body demand or defect in thyroid hormone receptors cause hypothyroidism. In several studies, hypothyroidism has been reported to be correlated

Name & Address of Corresponding Author
Dr. Rasika Hattewar
Department of Pediatrics,
Grant Govt Medical College,
Mumbai, India

with serum ferritin level; although in some studies there were no such correlations. Contrarily to significant iron deposition in thyroid gland, low activity remains about subclinical hypothyroidism. Thyroid dysfunctions are well documented in patients with thalassemia major requiring frequent and recurrent blood transfusion. These have recently been discussed in details in the literatures. Also, growth retardation is another complication that usually occurs. However, it almost will not happen with sequential transfusion. Nonetheless, defroxamine overuse causes growth retardation by itself . Although many studies report endocrinopathy in thalassemic patients, results are controversial and different, according to genetic and geographic characteristics of states, thus, we decided to study the pediatric patients admitted in St Georges Hospital , Mumbai to introduce hypothyroidism in correlation with short stature, regular transfusion and chelation therapy and serum ferritin level in this patients. Thyroid functions in chronically transfused children with BTM in the second decade of life have been studied, but there are very few studies evaluating the thyroid function in chronically transfused children in the first decade of life.

MATERIALS AND METHODS

A prospective study was conducted in the department of paediatrics, St Georges Hospital, Mumbai. The study was conducted on diagnosed patients of thalassemia major admitted to the paediatric ward. Duration of the study was 3 months. Taking into consideration of availability of patients within data collection period, a total of 32 children, diagnosed with β thalassemia major were enrolled in the study. All the necessary information regarding the study was explained to the parents and informed written consent was taken from the parents who were willing to participate in the study. After obtaining written informed consent in local vernacular language, the patients who were fulfilling the inclusion criteria were included in the study.

Inclusion Criteria

All admitted patients of thalassemia major aged 15 years and below.

Exclusion criteria

1. Very sick children
2. Those suffering from malnutrition
3. Chronic haemolytic anemia apart from thalassemia major
4. Those who are already taking iron or thyroid medications
5. Autoimmune thyroiditis was ruled out by antithyroid peroxidase and antithyroglobulin antibody testing.

Statistical Analysis

All the data collected were entered in to a spread sheet on Microsoft office Excel Sheet and then transferred to SPSS IBM version 21.0 for analysis. Significance of p value was taken as $p<0.001$.

RESULTS

The mean age of the studied thalassemia patients was 11.328±2.408 years with gender preponderance being 56.3% female children and 43.8 male children [Figure 1]. Incidence in less than 9 years old children was 21.9 %, while those more than 9 years were 78.1% of the total sample size [Figure 2]. Mean (SD) Sr. Ferritin levels was 3253.84 ±1142.67 ng/ml, mean (SD) free T3 level was 3.469 ±0.978pg/ml, mean (SD) free T4 levels was 1.658 ±1.142 pg/ml, mean (SD) TSH levels was 5.057 ±1.738 uIU/ml, and was not found to be statistically significant ($p > 0.001$).

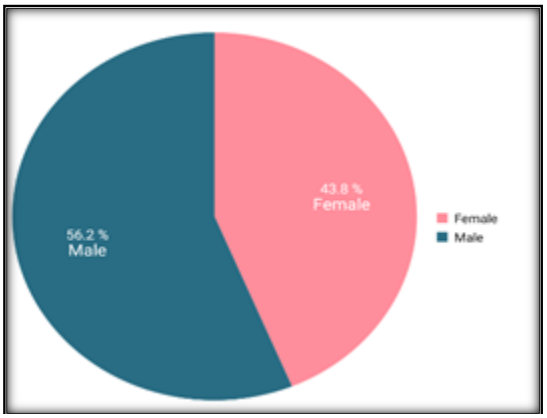

Figure 1: ?

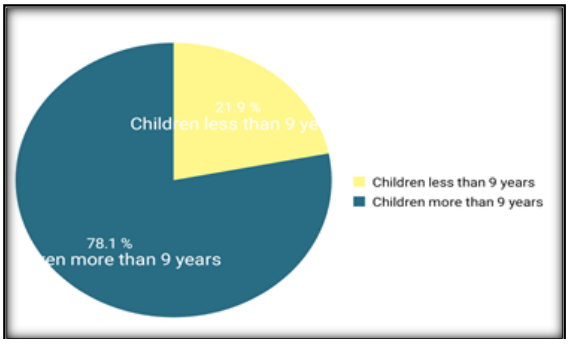

Figure 2: ?

Descriptive Statistics

	Number	Minimum	Maximum	Mean	Sd
Free T3	32	1.390 PG/ML	5.010 PG/ML	3.469 PG/ML	0.978 PG/ML
Free T4	32	0.67 PG/ML	7.76 PG/ML	1.658 PG/ML	1.142 PG/ML
TSH	32	1.640 uIU/ML	8.550 uIU/ML	5.057 uIU/ML	1.738 uIU/ML
SR. Ferritin	32	579.80 NG/ML	5695.00 NG/ML	3253.84 NG/ML	1142.67 NG/ML
Valid Number (N)	32				

Group Statistics

	Sex	Number	Mean	SD	P-value
Free T3 (PG/ML)	Male	18	3.368	0.897	0.515 (NS)
	Female	14	3.600	1.095	
Free T4 (PG/ML)	Male	18	1.425	0.290	0.195 (NS)
	Female	14	1.958	1.681	
TSH (uIU/ML)	Male	18	5.506	1.635	0.098 (NS)
	Female	14	4.480	1.751	
SR. Ferritin (NG/ML)	Male	18	3279.15	1192.73	0.890 (NS)
			3221.28	1118.58	

Group Statistics

	Age group	Number	Mean	SD	P-Value
Free T3 (PG/ML)	<9 years	7	3.611	1.130	0.672 (NS)
	>9 years	25	3.430	0.954	
Free T4 (PG/ML)	<9 years	7	2.244	2.439	0.127 (NS)
	>9 years	25	1.494	0.263	
TSH (uIU/ML)	<9 years	7	4.051	1.263	0.083 (NS)
	>9 years	25	5.339	1.767	
SR. Ferritin (NG/ML)	<9 years	7	3344.28	1248.68	0.817 (NS)
	>9 years	25	3228.51	1137.40	

DISCUSSION

Mean (SD) Sr. Ferritin levels was 3253.84 ±1142.67 ng/ml , mean (SD) free T3 level was 3.469 ±0.978 pg/ml, mean (SD) free T4 levels was 1.658 ±1.142 pg/ml , mean (SD) TSH levels was 5.057 ±1.738 uIU/ml, and was not found to be statistically significant ($p > 0.001$).

BTM children on regular transfusions and suboptimal chelation are at an increased risk for iron overload. Like in all organs, iron is deposited in the thyroid interstitium resulting in thyroid hemosiderosis. This slowly leads to worsening of the thyroid function. This study aims to analyze the type of thyroid dysfunction and its association with duration and amount of blood transfusions, serum ferritin level, and adequacy of chelation. Iron deposition from repeated transfusions has been implicated as the likely mechanism causing thyroid dysfunction in beta thalassemia major patients. Serum ferritin has a direct correlation to iron accumulation in the liver. Serum ferritin being an acute phase protein is also a product of hepatocellular damage. As a result, sepsis, congestive heart failure, and hepatitis can result in a falsely elevated measurement. No patients involved in our study have any clinical evidence of hepatitis or heart failure.

Our study aimed at evaluating thyroid function in chronically transfused children with Beta Thalassemia Major in the first and second decade of life. The study population consisted of 18 boys (56.3%) and 14 girls (43.8%). The influence of factors like duration and amount of blood transfusions, serum ferritin level, and iron chelation therapy on thyroid function was evaluated. Thyroid function was assessed using ELISA kits for the estimation of TSH, Free T4, and the iron overload was estimated by measuring the serum ferritin levels. In this study 7 children (21.9%) belonged to the first decade and 25 children (78.1%) belonged to the second decade of life [Figure 2]. Among them 56.3% were males and 43.8 % were females [Figure 1]. Subclinical hypothyroidism was the most common thyroid dysfunction observed in our study.

No correlation was found between gender, oral chelation, amount and duration of blood transfusion, and age at diagnosis with pattern of thyroid dysfunction. In our study, 4 out of 32 children (12.5%) had evidence of subclinical hypothyroidism with elevated levels of TSH. Among them one was a female and the other three were males. Two children belonged to the first decade and the other two to the second decade of life. All the 4 children received regular blood transfusions and oral iron chelation therapy. This is similar to other published studies done by Sharma et al.[15] and Abdel-Razek et al,[16] where subclinical hypothyroidism was most frequently reported. There was no evidence of autoimmune thyroiditis in children with thyroid dysfunction in our study. Few studies like the ones done by Soliman AT et al.[17] and De Sanctis et al.[18] showed prevalence of Central Hypothyroidism among beta thalassemia major children in the second decade of life.

All the children with thyroid dysfunction had high serum ferritin levels despite chelation with a mean ferritin value of 3253.84 ± 1142.67 ng/ml. The mean TSH value among the thyroid dysfunction group was 5.057 ± 1.738 mIU/ml. The mean Free T4 value among the thyroid dysfunction group was 1.658 ± 1.142 ng/dl.

Regular monitoring of thyroid function from the first decade of life will have a significant change in arresting the thyroid hemosiderosis and the thyroid dysfunction thereafter. Further, annual evaluation of thyroid function in beta thalassemia major children and the initiation of hormone replacement if found deficient will be beneficial.

CONCLUSION

We can conclude that thyroid function can be deranged among β-thalassemia major patients on

repeated blood transfusion due to iron deposition on thyroid gland. The most common abnormality in thyroid function in chronically transfused beta thalassemia major children is subclinical hypothyroidism. No correlation was found between thyroid dysfunction and factors like duration and amount of blood transfusions, serum ferritin level, and iron chelation therapy. Hence, it is important to do thyroid profile in these children on regular basis. We should try to screen all B-thalassemic children for thyroid hormone abnormalities, Serum ferritin levels as well. Enzyme therapy can be started with children with beta thalassemia major to prevent subclinical hypothyroidism.

REFERENCES

1. Rund D, Rachmilewitz E. Beta-thalassemia. The New England Journal of Medicine. 2005;353(11):1135–1146.
2. Sanctis VD, Eleftheriou A, Malaventura C. Prevalence of endocrine complications and short stature in patients with thalassaemia major: a multicenter study by the Thalassaemia International Federation (TIF). Pediatric Endocrinology Reviews, 2004; 2(2):249–255
3. Landau H, Matoth I, Landau-Cordova Z, Goldfarb A, Rachmilewitz EA, Glaser B. Cross-sectional and longitudinal study of the pituitary-thyroid axis in patients with thalassaemia major. Clinical Endocrinology. 1993; 38(1):55–61.
4. Cavallo L, Licci D, Acquafredda A et al. Endocrine involvement in children with β-thalassaemia major. Transverse and longitudinal studies. I. Pituitary-thyroidal axis function and its correlation with serum ferritin levels. Acta Endocrinologica. 1984; 107(1): 49–53.
5. Telfer PT, Warburton F, Christou S et al. Improved survival in thalassemia major patients on switching from desferrioxamine to combined chelation therapy with desferrioxamine and deferiprone. Haematologica. 2009; 94(12):1777-1778.
6. Multicentre study on prevalence of endocrine complications in thalassaemia major. Clinical Endocrinology. 1995; 42(6):581–586.
7. Jaruratanasirikul S, Wongcharnchailert M, Laosombat V, Sangsupavanich P, Leetanaporn K. Thyroid function in β-thalassemic children receiving hypertransfusions with suboptimal iron-chelating therapy. Journal of the Medical Association of Thailand. 2007; 90(9):1798–1802.
8. Telfer PT, Prestcott E, Holden S, Walker M, Hoffbrand AV, Wonke B. Hepatic iron concentration combined with long-term monitoring of serum ferritin to predict complications of iron overload in thalassaemia major. British Journal of Haematology. 2000; 110(4):971–977.
9. Filosa A, Maio SD, Aloj G, Acampora C. Longitudinal study on thyroid function in patients with thalassemia major,. Journal of Pediatric Endocrinology and Metabolism. 2006; 19(12):1397–1403.
10. Garadah TS, Mahdi NA, Jaradat AM, Hasan ZA, Nagalla DS. Thyroid function status and echocardiographic abnormalities in patients with beta thalassemia major in Bahrain. Clinical Medicine Insights: Cardiology. 2013;7:21–27.
11. Mula-Abed WS, Pambinezhuth FB, Al-Kindi MK, Al-Busaidi NB, Al-Muslahi HN, Al-Lamki MA. Congenital Adrenal Hyperplasia due to 17-alpha-hydoxylase/17,20-lyase Deficiency Presenting with Hypertension and Pseudohermaphroditism: First Case Report from Oman. Oman Medical Journal. 2014; 29(1):55–59.
12. Karamifar H, Shahriari M, Sadjadian N. Prevalence of endocrine complications in β-thalassaemia major in the Islamic Republic of Iran. Eastern Mediterranean Health Journal. 2003; 9(1-2): 55–60.
13. Zervas A, Katopodi A, Protonotariou A et al. Assessment of thyroid function in two hundred patients with β-thalassemia major. Thyroid. 2002; 12(2):151–154.
14. Eshragi P, Tamaddoni A, Zarifi K, Mohammadhasani A, Aminzadeh M, Thyroid function in major thalassemia patients: Is it related to height and chelation therapy?. Caspian Journal of Internal Medicine. 2011; 2(1):189–193.
15. Sharma R, Seth A, Chandra J et al. Endocrinopathies in adolescents with thalassaemia major receiving oral iron chelation therapy. Paediatrics and International Child Health. 2016; 36(1):22–27.
16. Abdel-Razek, A, Abdel-Salam MM, El-Sonbaty, Youness ER. Study of thyroid function in Egyptian children with β-thalassemia major and β-thalassemia intermedia. Journal of the Egyptian Public Health Association. 2013; 88(3): 148–152.
17. Soliman A, Al Yafei F, Al-Naimi L et al. Longitudinal study on thyroid function in patients with thalassemia major: High incidence of central hypothyroidism by 18 years. Indian Journal of Endocrinology and Metabolism. 2013; 17(6):1090.
18. Sanctis VD, Soliman A, Candini G, Campisi S, Anastasi S, Iassin M. High prevalence of central hypothyroidism in adult patients with β-thalassemia major. Georgian Medical News. 2013;222:88–94.
19. Aydinok Y, Darcan S, Polat A et al. Endocrine complications in patients with beta-thalassemia major. Journal of Tropical Pediatrics. 2002; 48(1)50.
20. Pirinççioğlu AG, Deniz T, Gökalp D, Beyazit N, Haspolat K, Söker M. Assessment of thyroid function in children aged 1-13 years with beta-thalassemia major. Iranian Journal of Pediatrics. 2011; 21(1): 77–82/

How to cite this article: Dhale S, Hattewar R, Kure S. Study of Thyroid Function Tests in Beta Thalessemia Major Patients in Children with Referance to Serum Ferritin Levels. Ann. Int. Med. Den. Res. 2020; 6(6):PE11-PE14.

Source of Support: Nil, **Conflict of Interest:** None declared