High prevalence of central hypothyroidism among patients with transfusion dependent thalassemia in Hospital Pulau Pinang: A cross sectional study

Chu Ee Seow, MD[1], Ai Sim Goh, MRCP[1], Shueh Lin Lim, MRCP[2]

[1]Haematology Unit, Department of Medicine, Penang Hospital, Penang Hospital, [2]Endocrine Unit, Department of Medicine, Penang Hospital

ABSTRACT

Introduction: Thalassemia is the most common heritable haematological disorder in Malaysia. Hypothyroidism is one of the complications of the transfusion dependent thalassemia (TDT) patients as a result of iron overload.

Materials and Methods: All registered TDT patients attending Haematology day care, Hospital Pulau Pinang from January 2019 to January 2020 were included in the study. Hypothyroidism was defined according to TSH and FT4, or based on the history of treatment for diagnosed hypothyroidism.

Results: There were 51 TDT patients, with 24 (47%) males and 27 (53%) females. Most of the patients were Malays (27, 53%) followed with Chinese (23, 45%) and Indonesian (1, 2%). Beta thalassemia major and HbE beta thalassaemia accounted for 35 (68.8%) and 14 (27.5%) TDT patients respectively, while two (3.9%) were HbH Constant Spring. Eleven (21.6%) had hypothyroidism; of which seven (63.6%) had central hypothyroidism, three (27.3%) had subclinical hypothyroidism, the remaining one (9.1%) had primary hypothyroidism. Three (27.3%) had concomitant hypogonadism, one (9.1%) had hypocortisolism and another (9.1%) had both diabetes mellitus and hypogonadism. There was no statistical relationship between the prevalence of hypothyroidism and age, serum ferritin, splenectomy history and iron chelation therapy.

Conclusion: High prevalence of central hypothyroidism is reported. Measurement of both TSH and FT4 is recommended as initial screening for thyroid dysfunction among patient with TDT.

KEYWORDS:
Transfusion dependent Thalassemia, hypothyroidism, prevalence

INTRODUCTION

Thalassaemia represents a heterogeneous group of recessively inherited haemoglobin disorder characterised by defective synthesis of one or more globin chains. The World Health Organization (WHO) estimates about 56,000 births are affected with major thalassaemia annually and at least 30,000 are transfusion dependent.[1] The total number of living Thalassemia patients in Malaysia is 7984 according to the Malaysia Thalassemia Registry updated in November 2018. HbE-beta thalassaemia forms the majority of thalassaemia patients in Malaysia with 2744 patients (34.37%), followed by beta thalassaemia major with 2676 patients (33.52%), HbH disease with 1458 patients (18.26%), beta thalassaemia intermedia with 748 patients (9.37%), while the remaining 358 patients (4.48%) have others forms of haemoglobinopathies.[2]

Thyroid dysfunction is a frequently occurring endocrine complication among transfusion dependent thalassemia (TDT) patients. The prevalence of hypothyroidism ranges from 4-29% in various countries, largely in the form of subclinical hypothyroidism.[3-8] High incidence of central hypothyroidism among thalassemia major patients was observed in some centers.[9,10] Tan K.A et al., reported the prevalence of hypothyroidism among Malaysian children with TDT, including subclinical and overt hypothyroidism as 18.3%.[11] Hypothyroidism among TDT patients is associated with iron overload,[12-14] which is the primary therapeutic complication for polytransfused thalassaemic patients, and is linked to hemosiderosis of thyroid and pituitary gland.[15]

Screening for thyroid dysfunction among TDT patients should be performed annually, beginning at the age of nine years old.[16] Most of the laboratory guidelines recommend a two-step approach (the thyroid cascade) in screening for thyroid dysfunction; in which TSH should be measured first, followed by free thyroxine (FT4) only if TSH is out of reference range.[18-21] In this study, we explore the adequacy of screening for hypothyroidism among TDT patient by using the similar approach.

MATERIALS AND METHODS

This is a retrospective cross-sectional study carried out on all TDT patients aged 18 years and above at the Haematology unit, Hospital Pulau Pinang. All thalassaemic patients who received 2-6 weekly transfusions in the Haematology Unit day-care were included in this study. The study looked into demographic data, data on ferritin level, iron chelation therapy, history of splenectomy and thyroid function profile from January 2019 to January 2020 over a period of 13 months. For TDT patient with hypothyroidism, data on the age of diagnosis hypothyroidism and associated endocrinopathies were analysed.

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Corresponding Author: Chu Ee Seow
Email: jmy_e@hotmail.com

Table I: Demographic data of study population (n= 51)

Characteristic	Value	
	Number (n)	Percentage (%)
Gender		
Male	24	47.0%
Female	27	53.0%
Ethnic		
Malay	27	53.0%
Chinese	23	45.0%
Indian	0	0.0%
Others	1	2.0%
Classification of thalassemia		
Beta major	35	68.6%
HbE/ Beta	14	27.5%
Others	2	3.9%

*Mean±SD

Table II: Number of study population with Hypothyroid

	Number (n)	Percentage
Hypothyroid		
No	40	78.4%
Yes	11	21.6%

Table III: Clinical characteristics of TDT patients (both hypothyroidism and euthyroidism groups)

Parameters	Euthyroidism (n=40)		Hypothyroidism (n= 11)		
	Mean±SD		Mean±SD		p value
Age	30±7		28±6		0.400
Ferritin (ng/ml)	3012±3047		3902±2531		0.073
	n	Percentage	n	Percentage	
Splenectomy					0.466
Yes	14	35.0%	2	18.2%	
No	26	65.0%	9	81.8%	
Iron chelation therapy					0.372
Single iron chelation agent (Total)	15	37.5%	6	54.5%	
DFO	6	15.0%	2	18.2%	
DFP	5	12.5%	4	36.3%	
DFX	4	10.0%	0	0.0%	
Two iron chelation agents (Total)	25	62.5%	5	45.5%	
DFO+DFP	20	50.0%	5	45.5%	
DFO+DFX	4	10.0%	0	0.0%	
DFP+DFX	1	2.5%	0	0.0%	

Table IV: Clinical characteristics of TDT patients with Hypothyroid (n= 11)

Characteristic	Number (n)	Percentage (%)
Mean age of diagnosis (years)	22.8±6.9*	
Hypothyroid subtype		
Primary	1	9.1%
Subclinical	3	27.3%
Central	7	63.6%
On treatment for Hypothyroid		
Yes	3	27.3%
No	8	72.7%
Associated endocrinopathies		
Hypogonadism	3	27.3%
Hypocortisolism	1	9.1%
Diabetes mellitus and Hypogonadism	1	9.1%

Table V: Hypothyroidism rate among TDT patients reported in various centres

Centre/country	Hospital Pulau Pinang	Indonesia[28]	India[26]	Malaysia (UMMC)[11]	Greece[5]	Pakistan[27]	Iran[8]
Age (years)	29.7±6.9*	10.8±4.1*	9.0±4.6*	13.7 (2.5-25.3)**	23.6±6.8*	7.6±2.5*	21.0±7.8*
Hypothyroid (Total)	21.6%	26.8%	15.6%	16.5%	16.5%	25.7%	14.6%
Primary	2.0%	1.7%	0.0%	3.7%	4.0%	1.4%	1.5%
Subclinical	5.9%	25.1%	10.0%	13.4%	12.5%	24.3%	10.8%
Central	13.7%	0.0%	5.6%	1.2%	0.0%	0.0%	2.3%

*Mean±SD
**Median (Range)

Ethical approval and informed consent for this study was approved by the Medical Research and Ethics Committee, Malaysia (approval NMRR no. NMRR-20-968-53107).

Hypothyroidism was defined according to TSH and FT4, or based on the history of treatment with levothyroxine for previously diagnosed hypothyroidism. Thyroid dysfunction was defined as follows: primary hypothyroidism (FT4 <12pmol/L with TSH >5mIU/L), subclinical hypothyroidism (normal FT4 with TSH >5mIU/L), and central hypothyroidism (FT4 is <12pmol/l with low or normal TSH).[10] Thyroid function test was routinely performed on all TDT patients at six monthly intervals. At least two consistent abnormal measurements of thyroid hormones were taken into account for the newly diagnosed hypothyroid cases, in order to reduce the possibility of misdiagnosing hypothyroidism due to individual circadian variation of secretion of thyroid hormone.[22,23]
Data were analysed using Statistical Package for Social Sciences (SPSS) software version 26, independent t-test and Fisher's exact test. Numerical data were presented as mean±standard deviation (SD). A p-value <0.05 was considered significant.

RESULT

This study surveyed all 51 TDT patients receiving regular transfusion under Haematology Unit day-care, in Hospital Pulau Pinang, 24 (47%) were males and 27 (53%) females. Most of the patients were Malays (27, 53%) followed with Chinese (23, 45%) and Indonesian (1, 2%). Their mean age at the time of study was 29.7±6.9 years. Beta thalassemia major and HbE beta thalassaemia accounted for 35 (68.8%) and 14 (27.5%) TDT patients respectively, while the remaining two (3.9%) were HbH Constant Spring (Table I).

As shown in Table II, eleven (21.6%) of the 51 patients, with a median age of 30.6±6.2 years, had hypothyroidism. Out of these 11 patients, seven (63.6%) had central hypothyroidism, three (27.3%) had subclinical hypothyroidism, while another (9.1%) had primary hypothyroidism. Mean age for TDT patients with hypothyroidism was 28±6years, appeared to be younger as compared to 30±7years for the euthyroidism group. There was no statistical relationship between the two groups (95% Confidence Interval, 95%CI: -6.8, 2.8).

The relationship between ferritin level, iron chelation therapy, splenectomy and hypothyroidism were analysed. The mean ferritin level was 3902±2531ng/ml for the hypothyroidism group. A higher ferritin level trend of was observed among TDT patients with hypothyroidism, compared to the euthyroid group who had mean ferritin level of 3012±3047ng/ml, however the relationship was not statistically significant (95%CI: -250.8, 5340).

The iron chelation regimen was divided into monotherapy or combination therapy. The monotherapy regimen included either Desferrioxamine (DFO), Deferiprone (DFP) or Deferasirox (DFX); combination therapy on the other hand consisted of DFO plus DFP, DFO plus DFX or DFP plus DFX. As shown in Table III, for TDT patients with normal thyroid function, 15 (37.5%) were on monotherapy, another 25 (62.5%) were on combination therapy. Meanwhile, six (54.5%) patients were on monotherapy, and another five (45.5%) were on combination therapy under the group with hypothyroidism. Data analysis failed to show statistical relationship between iron chelation therapy and hypothyroidism (p=0.327).

Out of the 40 TDT patients who were euthyroid, 14 (35%) had history of splenectomy; only two (18.2%) of the hypothyroidism group were splenectomised. Statistically, there was no significant relationship between splenectomy and hypothyroidism (p=0.466). The prevalence of other endocrine complications was also reviewed among TDT patients with hypothyroidism; three (27.3%) of them had hypogonadism, one (9.1%) had hypocortisolism and another (9.1%) had concomitant diabetes mellitus and hypogonadism (Table IV).

DISCUSSION

Combination of blood transfusion and iron chelation therapy significantly improve the life expectancy of TDT patients. Iron overload among polytransfused thalassaemic patients is associated with multiple endocrine complications, including hypogonadism, short stature, osteoporosis, adrenal insufficiency, hypoparathyroidism, hypothyroidism, diabetes mellitus and impaired glucose tolerance.[16,24] Differences in the age of first exposure to iron chelation therapy, the degree and type of chelation, the haemoglobin level attained before blood transfusion, and the continuing improvement in survival in well-chelated patients are among the factors that complicate the ascertainment of prevalence of endocrine complications.[17] Thus, wide ranges of hypothyroidism prevalence among TDT patients have been reported, from 4-29 % among different centers.[3-8] Routine screening for hypothyroidism among TDT patients is essential, as the classical clinical signs of hypothyroidism in TDT patients are subtle, non-specific and are frequently attributed to anaemia or associated diseases, especially for mild cases.[25]

Eleven (21.6%) TDT patients were reported to have hypothyroidism. Our centre reported 7 (13.7%) of central hypothyroidism, which is higher compared to most of the other centres in Indonesia (0%), India (5.6%), Greece (0%), Pakistan (0%) and Iran (2.3%) and another centre in Malaysia (1.2%), as shown in Table V. In fact, most of the other centres reported higher incidence of subclinical hypothyroidism.[6,8,11,26-28] High prevalence of central hypothyroidism among TDT patients was also reported by Soliman et al.,[9] which is linked to slow progressive dysfunction of the thyroid gland with pituitary insensitivity to the low FT4 level. Pituitary hemosiderosis significantly correlates with serum ferritin level.[31] The anterior pituitary gland is particularly sensitive to iron deposition and free radical oxidative stresses. Even a modest amount of iron deposition within the anterior pituitary can interfere with its function.[31-33] In terms of screening for hypothyroidism, most of the studies and laboratory guidelines recommend TSH as sole initial screening test for thyroid dysfunction, to reduce unnecessary burden on patients and health care systems from economic point of view.[17,18,21] However, normal TSH does not reflect euthyroidism in pituitary disease, including central hypothyroidism among TDT patients.[21] Thus, both FT4 and TSH are necessary in screening for hypothyroidism among TDT patients, as recommended in WHO guidelines for TDT.[16]

Advanced age is reported to be associated with hypothyroidism among TDT patients.[3,10,28] This can be linked to defective hypothalamic-pituitary-thyroid axis in the secretion of thyroid hormones over time. Relationship between hypothyroidism and serum ferritin level varies among different studies, Al-Hader et al., and Chirico et al., reported high prevalence of hypothyroidism correlates with high ferritin level.[14,15] Similar to other studies, this study shows no statistical relationship between ferritin level and hypothyroidism[3,10,28] One of the limitations in our study is that we did not look into the hypothyroidism risk factors in the past, including age of first exposure to iron chelation therapy, pre-transfusion haemoglobin level attained, previous intensity and type of iron chelation.

Previous studies have shown that good compliance to iron chelation therapy reduces prevalence of endocrinopaties, including hypothyroidism.[7,34] Our study shows no correlation between hypothyroidism and mono or combination iron chelation therapy (p=0.327), which was a similar finding to a study by Bazi et al.[3] Splenectomy was identified as one of the risk factors for hypothyroidism among TDT patients in some studies.[3,34] Belhoul et al., reported higher serum ferritin level among TDT patients with splenectomy history.[35] The finding may be related to the role of intact spleen as reservoir of excess iron as well as scavenging effect on iron free fractions, including non-transferrin bound iron.[10,35] In this study, there was no statistical relationship between prevalence of hypothyroidism and age, serum ferritin, iron chelation therapy as well as splenectomy history. This is probably related to our small sample size, which is the limitation of this study.

Other endocrinopathies were also observed among the TDT patients with hypothyroidism in this study, including three (27.3%) cases of hypogonadism, one (9.1%) case of hypocortisolism and another one (9.1%) with co-existence of diabetes mellitus and hypogonadism. These associated endocrinopathies were reported in other studies as well, which is related to iron overload from regular packed cells transfusions.[3,4,5,34]

CONCLUSION

High prevalence of hypothyroidism with predominance central hypothyroidism was reported in our study. Early detection and treatment of hypothyroidism in polytransfused thalassaemic patients is crucial as part of the holistic management of the disease. Dependence on TSH as the sole initial screening of thyroid dysfunction might miss out central hypothyroidism cases. Hence, measurement of both TSH and FT4 is recommended during the initial screening for thyroid dysfunction among patient with TDT.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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