Prevalence of endocrine complications in transfusion dependent thalassemia in Hospital Pulau Pinang: A pilot study

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ABSTRACT

Introduction: Frequent blood transfusions results in iron overload and lead to multiple endocrine complications. In spite of improvements in iron chelation therapy, a significant number of transfusion dependent thalassaemia (TDT) patients still develop endocrine complications. The aim of this study is to evaluate the prevalence of various endocrine complications in our adult TDT patients and to study the correlation with serum ferritin and liver iron concentration (LIC).

Methods: A retrospective review of all TDT patients treated in Haematology Unit, Hospital Pulau Pinang (HPP) was conducted.

Results: Of the 45 adult TDT patients, 22 were males and 23 were females with mean age of 28.8±6.9 years old. Majority of TDT in HPP were beta thalassemia major (71.1%), followed by E-Beta thalassemia (24.4%) and HbH-Constant Spring (4.4%). Frequency of transfusion was 3-4 weekly. 40.0% of adult TDT suffered from at least one endocrine complication. Among the adult TDT patients with endocrine complication, 50% have one endocrinopathy, 38.9% with two types of endocrinopathies and 11.1% of them have three or more types of endocrinopathies. Hypogonadism (22.2%) was the commonest endocrine complication, followed by osteoporosis (20%), hypothyroidism (13.3%), diabetes mellitus (6.7%) and hypocortisolism (4.4%). Patients with endocrine complications were significantly older. Mean serum ferritin level and LIC was higher among patients with endocrine complications but both were not statistically significant.

Conclusion: Endocrinopathy is still prevalent in 40% of adult TDT patients. This leads to higher health-care resource utilization, cost and significant morbidities among patients with TDT. Therefore, regular monitoring and early detection with intensification of chelation therapy is essential.

KEY WORDS:
Transfusion-dependent thalassemia, endocrine complications, iron overload, ferritin

INTRODUCTION

Thalassemia is a common genetic blood disorder which presents a substantial burden to patients and healthcare system especially in the developing countries.[1] Frequent blood transfusions results in iron overload and lead to multiple endocrine complications such as disorders of growth, sexual development and fertility, abnormal bone mineralisation, diabetes mellitus, hypothyroidism and hypocortisolism.[2] The aim of this study is to evaluate the prevalence of various endocrine complications in our adult transfusion dependent thalassaemia (TDT) patients and to study the correlation with serum ferritin and liver iron concentration (LIC).

MATERIALS AND METHODS

This was a retrospective cross-sectional study of all adult TDT patients treated in the Haematology Unit, Hospital Pulau Pinang (HPP) from January until December 2018.

Demographic data, types of thalassemia, history of iron chelation therapy, serum vitamin D level, serum ferritin, LIC from T2*MRI results and endocrine complications was retrieved from medical records of patients. Data was collected from January to February 2019.

Epi info version 7 was used to calculate the sample size. Based on other reported series, estimated sample size of 42 subjects would be adequate to determine a similar prevalence with a confidence level of 99%. Convenience sampling method was used to select a sample of 45 patients.

Hypogonadism was defined as the absence of testicular enlargement (<4mL) in boys or the absence of breast development in girls by the age of 16 years old and patients who were on hormone replacement therapy. Hypothyroidism was defined as overt hypothyroidism (high thyroid stimulating hormone [TSH] with low free thyroxine [FT4] level), subclinical hypothyroidism (TSH>5mU/L with normal FT4) and central hypothyroidism (low or normal TSH with low FT4). Patients were diagnosed with diabetes mellitus based on American Diabetes Association criteria. Osteopenia was defined as a T score between –1 and –2.5 and osteoporosis below –2.5 (World Health Organization Study Group, 1994). Adrenal insufficiency was defined as morning serum cortisol <100nmol/L with or without abnormal serum sodium and potassium or abnormal cortisol response during short synacthen stimulation test. Hypoparathyroidism was diagnosed when there was low serum calcium concentration, with increased serum phosphate and low serum intact parathyroid hormone. Vitamin D status was defined

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Table I: Demographic data of patients with transfusion dependent thalassemia

Characteristic	Value
Mean age (years) (±SD)	28.8±6.9
Gender	
Male, n(%)	22 (48.9)
Female, n(%)	23 (51.1)
Ethnic	
Malay, n(%)	23 (51.1)
Chinese, n(%)	21 (46.7)
Others, n(%)	1 (2.2)
Types of thalassemia	
Beta thalassemia major, n(%)	32 (71.1)
Haemoglobin E-Beta thalassemia, n(%)	11 (24.4)
Haemoglobin H-Constant pring thalassemia, n(%)	2 (4.4)
Mean age of diagnosis (years) (±SD)	3.64±4.35

Note: SD - Standard Deviation

Table II: Therapeutic characteristics

Therapeutic characteristics	Value, n(%)
Mean age of initiation of chelation (years) (±SD)	8.32±5.15
Chelation therapy	
Desferrioxamine	2 (4.4)
Deferiprone	9 (20)
Deferasirox	3 (6.7)
Desferrioxamine and Deferiprone	28 (62.2)
Desferrioxamine and Deferasirox	3 (6.7)
Pre-transfusion Hemoglobin >9g/dL	30 (66.7)
Serum Ferritin <2500µg/L	25 (55.6)
Patient with splenectomy	14 (31.1)

Table III: Endocrine complications among patients with transfusion dependent thalassemia

Endocrine Complications	No. of male patients	No. of female patients	Total No.
Osteoporosis	4	5	9 (20%)
Diabetes mellitus	1	2	3 (6.7%)
Hypothyroidism	3	3	6 (13.3%)
Hypocortisolism	1	1	2 (4.4%)
Hypogonadism	5	5	10 (22.2%)
Hypoparathyroidism	0	0	0 (0%)

Table IV: Risk factor for endocrine complications among patients with transfusion dependent thalassemia in Hospital Pulau Pinang

Variables	Endocrinopathies n=18	No endocrinopathies n=27	P value
Male, n (%)	8 (44.4)	14 (51.9)	0.626
Female, n (%)	10 (55.6)	13 (48.1)	0.626
Mean age in years (±SD)	32.4±6.6	26.4±6	0.006*
Mean serum ferritin µg/L	4075.4	3023.4	0.547
Pre-transfusion haemoglobin 9g/dL (±SD)	9.2±0.86	9.2±0.77	0.981
Liver iron concentration mg/g	14.1±11.86	10.6±10.55	0.233
Liver iron overload, n (%)	13 (72.2)	13 (48.1)	0.109
Myocardial iron concentration mg/g (±SD)	0.92±0.98	0.60±0.27	0.348
Age of initiation of chelation	8.25±5.59	8.36±4.95	0.718
Iron chelation			
Monotherapy	7 (38.9)	7 (25.9)	0.512
Combination therapy	11 (61.1)	20 (74.1)	0.512

Table V: Comparison with other case series

Endocrine Complications	Penang[5], 2008	Penang, 2018	Italy[3]	Saudi Arabia[6]	Sri Lanka[7]	Taiwan[8]	India[9]	Iran[10]	Dubai[11]
Mean Age (years)	23.1	28.8	50.3	12.2	11.8	17.2	17	13.3	15.4
Mean Serum Ferittin (µg/L)	4337	3444.2	777.1	3229.8	4083.3	-	2885.5	3801	2597.2
Osteoporosis (%)	36	22	-	-	-	17.4	-	-	
Diabetes mellitus (%)	8	6.7	18.6	1.2	7.4	21.2	4.7	7.8	10.5
Hypothyroidism (%)	0	13.3	27.9	14.8	25	8.8	4.7	7.8	6.5
Hypocortisolism (%)	4	4.4	0	0	2.1	-	-	-	-
Hypogonadism (%)	44	22.2	53.5	23.4	78.6	23.1	46	46.8	52.7
Hypoparathyroidism (%)	0	0	11.6	11.1	-	2	-	8.7	10.5

according to our laboratory reference ranges: Vitamin D deficiency was defined as serum vitamin D <50.0nmol/L; insufficiency was defined as 50.0-74.0nmol/L; sufficient levels were defined as 75.0-250.0nmol/L. Iron overload was assessed using the mean serum ferritin levels and the MRI T2*. Cardiac and liver T2* was assessed by a validated technique based on MRI relaxometry at 1.5T. The mean serum ferritin level during the study period in individual patient was calculated from latest readings available. Bone mineral density (BMD) was performed using Dual-energy x-ray absorptiometry (DXA) on L1–L4 lumbar spine and the hip.

Data was analysed using Statistical Package for Social Sciences software (version 21.0). Numeric variables were expressed as mean ± standard deviation and categorical variables were expressed as number and percentage. Mann-Whitney test was used to compare differences between two independent groups if the distribution were not normal. $p<0.05$ was considered statistically significant.

RESULTS

Patient characteristics

Of the 45 adult patients with TDT, 22 were males and 23 were females with mean age of 28.8±6.9 years old. Majority of TDT in our centre were beta thalassemia major (71.1%), followed by E-Beta thalassemia (24.4%) and HbH-Constant Spring (4.4%). 62.2% of our patients were on combination iron chelation therapy with desferroxamine and deferiprone while 31.1% were on monotherapy (Table I).

Therapeutic characteristic

Mean age of diagnosis for our patient was 3.6 years whilst the mean age of initiation of chelation was 8.3 years old. In all 66.7% of our patients were able to achieve pre-transfusion haemoglobin level of 9.0-10.5g/dL and 55.6% of TDT have serum ferritin <2500µg/L. More than thirty per cent of our patients had undergone splenectomy (Table II).

Prevalence of endocrine complications

In all 40.0% of adult TDT suffered from at least one endocrine complication. Among the adult TDT patients with endocrine complications, 50% have one endocrinopathy, 38.9% with two types of endocrinopathies and 11.1% of them have three or more types of endocrinopathies. Hypogonadism (22.2%) was the commonest endocrine complications, followed by osteoporosis (20%), hypothyroidism (13.3%), diabetes mellitus (6.7%) and hypocortisolism (4.4%). None of our patients had hypoparathyroidism. There was equal number of male and female patients with hypogonadism. Three out of six patients with hypothyroidism presented with subclinical hypothyroidism at mean age of 26.3 years old. One patient developed overt hypothyroidism at the age of 28 years old while two patients developed central hypothyroidism at age of 12 and 16 years old respectively. The summary of endocrine complications among our patients with transfusion dependent thalassemia is shown in Table III. In total 40.9% of our patients had vitamin D deficiency, 29.5% had vitamin D insufficiency and 29.5% had sufficient levels. However, there was no significant correlation between vitamin D level and osteoporosis. Table V shows the comparison of prevalence of endocrine complications with various reported series.

Risk factors for endocrine complications

Table IV shows the results of certain variables in relation to development of endocrine complications among patients with transfusion dependent thalassemia. Patients with endocrine complications in our centre were significantly older ($p=0.006$). Mean serum ferritin level and liver iron concentration was higher among patients with endocrine complications but both were not significantly different ($p=0.547$ and $p=0.233$). No significant difference was observed between patients with and without endocrine complications in the gender ratio, pre-transfusion haemoglobin level and myocardium iron load. There was a significantly positive correlation between serum ferritin level and liver iron concentration ($r=0.559$, $p<0.001$). No correlation was found between age of starting chelation therapy and type of chelation with endocrine complications.

DISCUSSION

Life expectancy of thalassemia patients has significantly increased due to improvement in monitoring and therapeutic methods, especially with intensive transfusion program combined with chelation therapy and imaging methods.[3,4] As a result, survival of patients on treatment with appropriate transfusion and chelation has increased to 40-60 years and is expected to extend soon to the geriatric age group.[3] High incidence of endocrine abnormalities were found among TDT patients worldwide which has led to a new set of challenges for both the patients and the treating team.

In this cross-sectional study, we found a high prevalence of endocrinopathies in our adult TDT patients, 40% of them have at least one endocrine complication. Hypogonadism is the most common endocrine complication in our study population which is a similar finding in other reported series.[5-11] Hypogonadism is likely to be caused by iron deposits in the gonads, pituitary gland or both. Iron deposition in the pituitary gonadotrope seems to be the main contributing factor to the development of hypogonadism. However, some studies found that hypogonadism in thalassemia is related not only to iron toxicity on gonadotrope cells but also to adipose tissue and leptin. Leptin is a polypeptide hormone produced by adipose cells, which acts as a signal to initiate puberty. Low leptin levels were observed among thalassemia patients in several studies.[12,13] Therefore, lower level of leptin may be one of the factors causing delayed puberty in thalassemia patients.

Osteoporosis is the second most common endocrine complication in our study cohort. Marrow expansion, various endocrine causes, iron chelators or direct iron toxicity have been identified as possible factors associated with low bone mass.[14] A total of 20% of our patients had osteoporosis and 55.6 % had osteopenia. In our study, statistically significant association was found between osteoporosis with diabetes mellitus ($p=0.006$) and hypogonadism ($p=0.017$). It is well known that sex hormones regulate skeletal maturation and preservation in both men and women. The impact of hypogonadism on skeletal integrity has been widely

recognized. Our findings was in agreement with several studies which show similar result of hypogonadism and osteoporosis in thalassemia patients.[15,16] 40.9% of patients had vitamin D deficiency, 29.5% had vitamin D insufficiency and 29.5% had sufficient levels. No association was demonstrated between osteoporosis and serum vitamin D level. We also found a correlation between osteoporosis and diabetes mellitus. It is likely that TDT patients who developed diabetes mellitus are not well chelated and hence have multiple endocrinopathies.

The prevalence of endocrine complications such as osteoporosis and hypogonadism has significantly improved over recently. The reasons for the improvement could be because of increased awareness of treating physicians, development of guidelines on monitoring and treatment of patients with TDT and advancement in treatment of iron overload.

Hypothyroidism is the third commonest endocrine complication in our cohort. This was in contrast with an earlier study done in our centre ten years ago in which no patient with hypothyroidism was reported.[5] A total of six patients with hypothyroidism were found in our study, with three of them requiring treatment with levothyroxine (one patient with overt hypothyroidism and two patients with central hypothyroidism). Most of them were diagnosed in the second decade of life. This finding is consistent with a study done by Soliman et al., in which 35% of their patients had worsening of thyroid function by 18 years old. Majority of their patients with hypothyroidism were due to central hypothyroidism.[17] Thus this highlights the importance of measuring both TSH and FT4 level as a screening test for hypothyroidism among patients with TDT as they can develop different spectrum of thyroid dysfunction at any point in their life. The screening for thyroid dysfunction should be done lifelong in this cohort. In addition, none of our patients with hypothyroidism had clinical thyroid enlargement and thyroid autoantibodies was not part of our initial screening, therefore it is difficult to ascertain the cause of hypothyroidism. It is interesting to note that our three patients with hypothyroidism on replacement treatment are well chelated with no iron overload. Different findings were reported by some studies in which hypothyroidism was reported to occur more commonly in severely anaemic or iron overloaded thalassaemics but was uncommon in optimally treated patients.[18,19] Further analysis should be done to look for other contributing factors.

In addition, we found that the mean serum ferritin level and liver iron concentration were higher among patients with endocrine complications, but both were not statistically significant. Serum ferritin is an acute phase reactant that fluctuates with inflammatory, infectious, and other stress conditions. Therefore, its reliability for the assessment of iron overload remains limited. Clinicians must interpret the level of serum ferritin cautiously as ferritin trends do not predict changes in total body iron and should not be used as the sole tool to assess iron overload.[20] Several studies have reported the similar poor correlation between serum ferritin and endocrine complications.[21-23] This could be related to iron toxicity in early life and suggest that serum ferritin is not a sensitive marker for iron overload.

There were several limitations in our study as it was a single centre study and the sample size was relatively small. A larger sample size of patients may demonstrate significant correlation between endocrine complications and levels of ferritin and liver iron concentration. The average of latest serum ferritin measurement and latest result of LIC could not fully represent the long-term impact of iron overload on endocrine complications. Furthermore, adherence of patients to iron chelation therapy was not addressed in the present study. However, we were able to follow up and compare the prevalence of endocrine complications of TDT from the same centre after ten years.

CONCLUSION

Despite of improvement in iron chelation therapy, endocrinopathy is still prevalent in 40% of adult TDT patients. This leads to higher health-care resource utilisation, cost and significant morbidities among patients with TDT. Patients with endocrinopathy showed a higher trend of serum ferritin and LIC. Therefore, regular monitoring and early detection with intensification of chelation therapy is essential. A large multi-centre study should be carried out and propose a local guideline for screening algorithm for endocrine system for patients with TDT.

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APPROVAL

Approval of the study was obtained from Malaysian Medical Research Ethics Committee (NMRR-19-482-46697).

CONFLICT OF INTEREST

None declared

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