THE PREVALENCE OF ENDOCRINOPATHIES AMONG PATIENTS WITH THALASSEMIA MAJOR IN THE DISTRICT OF BATTICALOA, SRI LANKA

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ABSTRACT

Introduction: Thalassaemia major is an inherited haemoglobinopathy characterised by chronic anaemia. Excessive iron overload and suboptimal chelation result in deposition of iron in various tissues including endocrine glands.

Objective: To estimate the prevalence of endocrinopathies in patients with thalassemia major among patients attending clinics at Teaching Hospital Batticaloa.

Materials and Methods: Cross sectional descriptive study of patients with thalassemia major on active follow up from June 2015 to 2016 at Teaching Hospital Batticaloa. Height, weight, and tanner staging, serum ferritin, oral glucose tolerance test, bone profile, liver and renal function, thyroid function, cortisol for all patients and FSH, LH, testosterone or oestradiol for girls over 13 years of age and boys over 14 years of age were assessed.

Results: A total of 95 patients including 50 females with the mean age of 11.83 ± 4.53 years were evaluated. Short-stature was found in 55(57.8%). Hypocalcaemia was present in 36(37.8%) and 24(25%) had hypothyroidism. Diabetes mellitus and impaired glucose tolerance (IGT) were found in 7(7.4%) and 13(13.2%) respectively. Only 2(2.1%) had cortisol deficiency. Among girls over 13 and boys over 14 years of age, 33(78.6%) had hypogonadism. Sixty six patients with mean serum ferritin level above 2500ng/mL had higher incidence of hypocalcaemia, hypothyroidism, hypogonadism, and short stature (28 vs 5; $p=0.004$, 18 vs 6; $p=0.048$, 28 vs 5; $p=0.03$, and 39 vs 16; $p=0.054$ respectively) than those who had less than 2500ng/mL. Patients who were above 9 years of age had higher incidence of hypocalcaemia (32 vs 2; $p=0.00$), short stature (33 vs 22; $p=0.026$), and IGT (11 vs 2; $p=0.017$) when compared to younger patients.

Conclusions: A significant proportion of thalassemia major patients have endocrinopathies. Hypothyroidism and short stature develop very early and other endocrinopathies also develop earlier indicating the need for early screening compared to the recommended guidelines. As the duration of thalassemia increases the risk for developing endocrinopathies is high.

Key Words: Thalassaemia major, endocrinopathy, diabetes mellitus and risk factors.

INTRODUCTION

Thalassaemia major is a severe autosomal recessive haemolytic anaemia caused by absence or marked deficiency of the beta globin chain of haemoglobin. The homozygous state results in severe anaemia which requires frequent blood transfusions. This, along with increased rate of iron absorption in the gut causes iron overload. Excessive iron overload due to suboptimal chelation result in deposition of iron in various tissues, primarily heart and liver and frequently involves endocrine glands. Chronic hypoxia due to anaemia, viral infections and individual susceptibility are other factors which could potentiate the toxicity of iron

deposition, contributing to endocrine dysfunction (1,2). Available data show the leading endocrine complications among patients with thalassaemia are growth retardation, hypogonadism, diabetes mellitus, hypothyroidism, hypoparathyroidism, osteoporosis and adrenal insufficiency (3).

In addition to iron overload, poor nutrition, chronic anaemia, chelating agents, liver disease, and genetic susceptibility are the other factors which have been linked to slow growth and endocrinopathies in patients with thalassaemia (4). As the prevention of thalassaemia related endocrinepathies remains a challenge, regular screening is recommended. However, it is not clear when this process should start

or what is the best procedure for conducting it, as the age of onset of these endocrinopathies is not well defined. Hence there is a need for estimating the prevalence of common endocrinopathies in patients with Thalassaemia and risk factors for developing these complications, among Sri Lankan population. Therefore, we designed this study to estimate the prevalence of common endocrinopathies in patients with Thalassaemia major who were followed up at Teaching hospital, Batticaloa.

METHODOLOGY

This is a descriptive cross sectional study. The study subjects were all patients with diagnosed Thalassaemia major on regular blood transfusion for more than 2 years duration, who were attending paediatric, haematology and endocrinology clinics at Teaching Hospital Batticaloa.

All patients who have full filled the selection criteria and given consent were included. Diagnosed patients with thalassaemia intermedia, thalassaemia minor, other haemoglobinopathies and other haemolytic anaemia were excluded from the study.

The study was approved by the ethical committee of eastern university and permission from the director, Teaching Hospital Batticaloa was obtained for utilising the data and conducting the study. All participants were given assurance that their identity will not be revealed and personnel information could be kept confidential. Informed written consent was obtained from all patients, their parents or guardians if participants are younger than 16 years.

Demographic data, details of disease management (duration and age at the start of transfusion and chelation), and auxological details (height, weight, tanner staging for pubertal development) were recorded in a data collection form by the trained medical officer.

The following hormonal assessment were done: TSH, freeT4, 9am cortisol for all patients and FSH, LH, prolactin, oestradiol or testosterone for girls over 13 years of age and boys over 14 years of age.

Biochemical assessment including oral glucose tolerance test (OGTT) using 75g glucose, serum calcium, phosphate, alkaline phosphatase, haemoglobin, mean serum ferritin, renal function, liver enzymes and liver function were taken.

Description of endocrinopathy (5)

- Short stature was defined as height below the third percentile and below the mid-parental height centile on the CDC growth chart.
- Delayed puberty was defined as absence of breast development by the age of 13 years in girls or absence of genital development (testicular volume less than 4ml) at 14 years in boys. Incomplete puberty is defined as primary amenorrhea in females at 17 years or failure to reach Tanner genitalia stage 5 in males by the age of 18 years.
- Patients with hypogonadism (delayed or incomplete puberty) and prepubertal basal follicular stimulating hormone (FSH) and luteinizing hormone (LH) levels were considered to have hypogonadotropic hypogonadism, and those with high basal FSH and LH levels were defined as having gonadal failure.
- Primary hypothyroidism was defined as subnormal free thyroxine (FT4) with raised thyroid stimulating hormone (TSH), subclinical hypothyroidism as normal FT4 with high TSH (5-10miu/l) and secondary hypothyroidism as subnormal FT4 with normal or subnormal TSH on more than 2 consecutive occasions.
- Hypoparathyroidism was defined as subnormal serum calcium with high phosphate with subnormal or inappropriately low parathyroid hormone (PTH) level.
- Patients were considered to have diabetes if their fasting glucose more than 126mg/dl and / or 2 hour post glucose level more than 200mg/dl. Impaired glucose tolerance was defined as 2 hour post glucose level of 140-199mg/dl and impaired fasting glucose when fasting glucose level of 100-125mg/dl.
- Adrenal insufficiency was defined as morning (9 am) serum cortisol less than 150nmol/L with or without abnormal serum sodium and potassium.

The data were analyzed using SPSS Statistical Software Package.

All numerical data were expressed as mean and standard error of mean ($\pm$ SEM). Correlation among variables was assessed using Chi square test. Statistical significance is described when p-value less than 0.05.

Table1: Demographic, auxological and biochemical variables of patients with thalassaemia major attending to Teaching Hospital Batticaloa, Sri Lanka.

Variable	Mean+/- SD	95% CI	Standard error
Age (Y)	11.83+/- 4.53	10.83 – 12.83	0.50
Weight (Kg)	26.58+/-9.51	24.48 – 28.68	1.05
Height (cm)	130.74+/-16.67	127.06 – 134.43	1.85
Ferritin level (ng/ml)	4083.3+/-2592.89	3509.96 – 4656.63	288.09
Duration of thalassaemia (Y)	10.42+/-4.33	9.46 – 11.38	0.48

RESULTS

A total of 95 patients including 50 females and 45 males with mean age of 11.83±4.53 years were evaluated. The characteristics of the patients are shown in table 1. The prevalence of endocrinopathies was shown in table 2 and 3. Short stature was found in 55 (57.8%). Among 42 patients who were evaluated for pubertal development, 33 (78.6%) had hypogonadism, and all were proven to be hypogonadotropic hypogonadism. Hypocalcaemia was present in 34 (35.7%) and 24 (25.2%) had hypothyroidism. Diabetes mellitus and impaired glucose tolerance (IGT) were found in 7 (7.4%) and 13 (13.6%) respectively. Only 2 (2.1%) had cortisol deficiency.

Among this sample, the youngest age for patients with endocrinopathies were as follows (table 4): hypothyroidism; 3years, short stature; 5years, hypocalcaemia; 9years, IGT; 9 years, diabetes; 10years and cortisol deficiency; 14years.

Sixty six patients with mean serum ferritin level above 2500ng/mL had higher incidence of hypocalcaemia than those who had less than 2500ng/mL (28 vs 5, $p=0.004$). Higher prevalence of hypothyroidism, hypogonadism, and short stature (18 vs 6; $p=0.048$, 28 vs 5; $p=0.03$, and 39 vs 16; $p=0.054$ respectively) was noted among patients with ferritin levels above 2500ng/mL.

Patients who were above 9 years of age had higher incidence of hypocalcaemia (32 vs 2; $p=0.00$), short stature (33 vs 22; $p=0.026$), and IGT (11 vs 2; $p=$ when compared to younger patients (0.017) . Although statistically not significant, prevalence of hypothyroidism (16 vs 8; $p=0.085$), and cortisol deficiency (2 vs 0; $p=0.118$) were higher among patients with longer duration of disease.

DISCUSSION

Thalassemia patients have a high prevalence of endocrinological abnormalities. Our study revealed that a significant proportion of thalassaemia major patients have endocrinopathies (table 2). The international network on endocrine complications in thalassemia (I-CET) position statement and guidelines recommend annual endocrine screening from the age of 9 years and earlier if clinically suspecting short stature. In our sample the youngest age of patient with endocrinopathies were shown in table 2. Although majority of children develop endocrine disorders after 9 years, 9 (9.4%) were younger than 9 years with either short stature or hypothyroidism. Growth retardation is commonly reported in children and adolescents with thalassaemia. The pathogenesis of growth failure is multifactorial including transfusion-related iron overload, chelation toxicity and other contributing endocrine disorders such as hypothyroidism, hypogonadism, growth hormone deficiency or insufficiency, zinc deficiency, chronic liver disease, under nutrition, and psychosocial stress (2,6,7). Our study showed 71(75%) were having body weight less than 3rd centile, and 55(57.5%) of children had height below the 3rd centile and below the mid-parental height centile on CDC growth chart. The limitations on using this charts for defining short stature should be considered in our population. This is due to the fact that a significant proportion of normal children are below 3rd centile. Therefore mid-parental height should be taken when defining short stature. In addition, the duration of thalassaemia was significantly associated with short stature. This is probably due to iron overload and failure of gaining their pubertal growth spurt. In our study 8(14.5%) were younger than 9 years old and the youngest was 5 years old.

Table 2: Comparison of prevalence of endocrinopathies between those with serum ferritin above 2500ng/mL and below 2500ng/mL among thalassemia patients attending to Teaching Hospital Batticaloa, Sri Lanka.

Endocrinopathies	No of patients with Ferritin>2500ng/mL	No of patients with Ferritin<2500ng/mL	Total No of patients (%)	P value (Pearson Chi Square)
Hypocalcaemia	28	5	34 (35.7%)	0.004
Hypothyroidism	18	6	24 (25.2%)	0.048
Hypogonadism	28	5	33 (78.6%)	0.03
Short stature	39	16	55 (57.8%)	0.054
IGT	11	2	13 (13.6%)	0.13
DM	5	2	7 (7.4%)	0.95
Cortisol deficiency	2	0	2 (2.1%)	0.65

Table 3 - Comparison of prevalence of endocrinopathies between those who are above 9 years and below 9 years of age among thalassemia patients attending teaching hospital Batticaloa, Sri Lanka.

Endocrinopathies	No of patients with age > 9 years	No of patients with age < 9 years	Total No of patients (%)	P value (Pearson Chi Square)
Hypocalcaemia	32	2	34 (35.7%)	0.000
Hypothyroidism	16	8	24 (25.2%)	0.085
Short stature	33	22	55 (57.8%)	0.026
IGT	11	2	13 (13.6%)	0.017
DM	4	3	7 (7.4%)	0.84
Cortisol deficiency	2	0	2 (2.1%)	0.118

Table 4 – Youngest age in the sample of patients with thalassaemia major attending to Teaching Hospital Batticaloa, Sri Lanka.

Endocrinopathy	Youngest Age (Y)
Hypothyroidism	3
Short stature	5
Hypocalcaemia	9
IGT	9
DM	10
Cortisol deficiency	14

One fourth of our patients had hypothyroidism. In our study, some patients were already treated with thyroxine based on elevated TSH or subnormal FT4 alone. Therefore we were unable to subcategorize the diagnosis as primary, secondary or subclinical hypothyroidism. Similar studies showed that majority of patients were diagnosed with primary hypothyroidism and secondary hypothyroidism seen only in 3.5% (8,9). The I-CET position statement and guidelines recommend annual investigation of thyroid function beginning at the age of 9 years (10). In our study 4 (16.6%) patients were below 9 years old when diagnosed with hypothyroidism and the youngest patients was 3 years of age. Hypothyroidism and short stature develop early in our population indicating the

need for early screening compared to the recommended guidelines.

Hypoparathyroidism is considered as an uncommon complication and usually presents after the age of 16 years (10). In contrary to this we found a significant proportion 34 (35.7%) was complicated with hypocalcaemia and hyperphosphataemia suggestive of hypoparathyroidism and the youngest age was 9 years in our sample. The majority of the patients was asymptomatic or presented with mild symptoms. Hypoparathyroidism is thought to be the consequence of iron deposition in the parathyroid glands or due to suppression of parathyroid secretion induced by bone reabsorption resulting from increased hematopoiesis secondary to the chronic anaemia (11,12). High serum

ferritin levels and the longer duration of thalassaemia were significantly associated with hypocalcaemia in this study.

Diabetes and impaired glucose tolerance (IGT) are relatively common complications among inadequately chelated patients. As life expectancy in patients with thalassaemia rises, diabetic complications are commonly seen. The prevalence of diabetes mellitus in patients with thalassaemia major ranges from 6.4 to 14.1% in cross sectional studies (13). This current study showed presence of Diabetes mellitus and IGT in 7.4% and 13.6% respectively. Patients with thalassaemia could develop diabetes secondary to their illness and complications of therapy. Likewise, with the worldwide epidemic of diabetes, they could develop type 1 or type 2 diabetes, independently of their thalassaemia status (14,15).

Although clinical adrenal crisis is extremely rare, several studies reported a significant prevalence of biochemical adrenal insufficiency, ranging from 0% to 45%, in patients with thalassaemia. The wide variation is due to different patient characteristics and different diagnostic tests used (16,17). Only 2 patients (2.1%) had cortisol deficiency in this study. Patients are usually asymptomatic but this could be masked by symptoms commonly complained by thalassemic patients, such as myalgias, arthralgias and weight loss. In addition to cortisol deficiency, adrenal androgen levels might be decreased explaining the poor development of pubic and axillary hair observed in thalassemic adolescents (16,17).

Comparable to other studies hypogonadism was the most common endocrinopathy in our patients (18-21). Out of 42 patients (28 female and 14 males) who were evaluated for pubertal development, the overall prevalence of hypogonadism was 78.6%, including 71% of girls and 92% of boys. All our patients had secondary hypogonadism with low basal FSH and LH indicating hypothalamic-pituitary damage. This is likely to be secondary to iron deposition on gonadotrophic cells of the pituitary gland (22-24). Among patients with thalassaemia major, an impact of the genotype on gonadal function also has been documented (25).

A significant proportion of thalassaemia major patients have endocrinopathies. The longer the duration of thalassaemia, the higher the risk for developing endocrinopathies. Hypothyroidism and short stature develop early and other endocrinopathies develop after 9 years of age, indicating the need for earlier screening compared to the recommended guidelines. For early

detection, regular follow-up is essential. Treatment of endocrine disorders in patients with thalassaemia is an additional burden, support from family, health care providers and psychologists are needed. Multidisciplinary team with patient centered approach will be the way forward. Joint clinic where members of both endocrinology and thalassaemia teams work together with patients will be a better option to manage these patients with complex needs. This also allows staff to learn from each other and provide a consistent approach towards every patient.

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DECLARATION OF INTEREST

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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