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STUDY OF ENDOCRINOLOGICAL COMPLICATIONS IN CHILDREN WITH BETA-THALASSEMIA MAJOR: A HOSPITAL BASE STUDY.

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ABSTRACT

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Background: Beta thalassemia major (TM) is the most common inherited genetic disorder worldwide. Patients are at risk of iron overload, which leads to various forms of tissue damage, including endocrinopathies.
Aim of the study: The aim of this study was to evaluate the prevalence and risk factors of endocrine disorders in Adolescent patients.
Methods: A prospective analytical study done was done at Bangladesh Shishu Hospital & Institute, Dhaka, Bangladesh from 1st October 2021 to 1st July 2022 among the diagnosed cases of Beta Thalassemia Major.
Result: Among 80 TM children, 32(44.19%) patients were female and 48(55.81%) were male. The mean (SD) patient age at the time of the study was 11.34 (2.27), range: 2–18 years and 11.12 (2.01) range: 2–12 in males and females, respectively. In those who received combined therapy, 6 of 17 (32.14%) cases had endocrine disorders, compared with 34 of 63 (53.97%) cases who did not have endocrine disorders.
Conclusion: Endocrinological complications in adolescent children with thalassemia major were mild in severity in our study and observed when the serum ferritin went beyond 2500 ng/ml. Early identification and multidisciplinary management are necessary for early recognition,treatment as well as prevention of endocrinological complicationsin patients with Thalassemia Major.

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INTRODUCTION

Beta thalassemia major (TM) is an autosomal recessive inherited disorder caused by decreased or absent β-globin chain production. There are 200 mutations linked with a TM phenotype that affect the stages of β-globin gene expression [1]. TM is the most prevalent monogenic disorder in the world, and the incidence rate is higher in the Middle East [2]. TM is the most common chronic hemolytic anemia in Egypt. It constitutes a major health problem with an estimated carrier rate of 9–10% [3]. TM brings long-term extravascular hemolysis, which increases iron absorption in the intestinal tract. Combined with multiple blood transfusions, this could lead to iron overload and an increased amount of iron in the tissue, which can cause progressive tissue damage in the liver, heart, endocrine glands, and other organs by generating hydroxyl free radicals and oxidative stress [4–6]. Treatment of TM is always individualized and modified according to the patient's conditions. Conventional treatment consists of regular transfusions, an iron chelating agent, splenectomy, supportive therapies, and psychological support [7]. Non-conventional treatment includes hematopoietic stem cell transplantation, which remains the only curative treatment, fetal hemoglobin modulation, and gene therapy [8, 9]. Furthermore, the life expectancy and the quality of life of TM has improved remarkably over the last decades following optimized transfusion programs and improvements in chelation therapy [10, 11]. However, patients still experience a range of problems, particularly in relation to their growth, development, malnutrition, transfusion-transmitted infections, and tissue damage such as in the liver, heart, and endocrine system. These factors may contribute to the morbidity and mortality of these patients [12]. Endocrinopathies are common in patients with TM despite parenteral and oral iron chelation therapy. A majority of studies have focused on endocrine disorders in the adult population over 12 years of age. Many of these reports are from the Mediterranean area, and few studies have been conducted in children and young adults from Asian populations [13–17]. These studies researched the efficacy of TM treatments in preventing endocrine disorders. There are no studies in the literature describing the possibility of endocrine disorders that may start early in TM patients before 12 years of age. Very few works have been done in this field in Bangladesh. The aim of this study was to evaluate the prevalence and risk factors of endocrine disorders in Adolescent Thalassemia Major Patients.

METHODOLOGY & MATERIALS

A prospective analytical study done was done at Bangladesh Shishu Hospital & Institute from 1st October 2021 to 1st July 2022 to determine the prevalence of endocrinological complications and their correlation with mean serum ferritin levels in beta thalassemia patients. During the study period, children who have been diagnosed as β thalassemia major by Hb electrophoresis, whose age is between 9-18 years and who are taking blood transfusion and iron chelation therapy at our centre were enrolled via purposive sampling, whose age was <9 years or >18 years and who are not taking regular blood transfusion at our centre were excluded from the study. Basic demographic features like age, sex, religion, caste, age of diagnosis, pretransfusion mean haemoglobin, annual blood requirement are recorded in a pre-structured proforma. Patients with age of starting iron chelation therapy, name of iron chelator, dose, and duration were also recorded in proforma. Growth data was plotted on WHO adjusted chart. Detailed general examination including anthropometry, ta nner staging/sexual maturity rating and detailed systemic examination was done and their findings were recorded in the pre-structured proforma. Investigations like complete hemogram, serum ferritin level, serum calcium, phosphate, ALP,

TSH with free T3 and T4, vitamin D3 levels, HbA1c done in all patients after enrolment. Serum TSH,LH, FSH and testosterone levels were done in children whose parents were willing for doing outside investigation as it was not done at our setup. Other investigations done as and when required. Data were analyzed using SPSS software version 14. All data are presented as mean±standard deviation and values of $p<0.05$ were considered statistically significant.

All data were presented in a suitable table or graph according to their affinity. A description of each table and graph was given to understand them clearly. All statistical analysis was performed using the statistical package for social science (SPSS) program, and Windows. Continuous parameters were expressed as mean ±SD and categorical parameters as frequency and percentage. Comparisons between groups (continuous parameters) were made by Student's t-test. Categorical parameters compared by Chi-Square test. The significance of the results as determined by a 95.0% confidence interval and a value of $P<0.05$ was considered to be statistically significant.

RESULT

Among 80 TM children, 32(44.19%) patients were female and 48(55.81%) were male. The mean (SD) patient age at the time of the study was 11.34 (2.27), range: 2–18 years and 11.12 (2.01) range: 2–12 in males and females, respectively. The mean (SD) duration of the disease was 5.74 (3.45) and 5.14 (3.20) in males and females, respectively. Patient's anthropometric measurements, iron chelation therapy pattern and other patient characteristics are shown in Table 1. Most of the patients had no endocrine disorders (68/80, 85.00%; Table 2). The presence of any endocrine disorder was observed in 12/80 (15.00%) patients. However, the most common endocrine disorders were subclinical hypothyroidism 2/80 (0.96%) and clinical hypothyroidism 2/80 (0.96%), followed by abnormalities in glucose homeostasis 9/120 (7.5%), and none of them had diabetes mellitus (DM). As shown in Table 3, the presence of endocrine disorders in the studied population was not significantly associated with the risk factors age, gender, hemoglobin level before transfusion, or splenectomy status ($P > 0.05$).. However, there were a significant increase in the mean (SD) serum ferritin levels in the studied TM patients with endocrine disorders 3631.45 (1636) µg/L when compared with the studied TM patients without endocrine abnormalities 2658.40 (1443) µg/L). Regarding iron chelating therapy, there were no significant change between patients with or without endocrine disorders regard monotherapy started with deferasirox or desferoxamine. However, in those who received combined therapy, 6 of 17 (32.14%) cases had endocrine disorders, compared with 34 of 63 (53.97%) cases who did not have endocrine disorders, (Table 3).

Table 1: Characteristics of the study population.

Characteristics	Summary statistics Total 80 patients				Total	
	Male 48 (55.81%)		Female 32(44.19%)			
	N	%	N	%	N	%
Age / years						
Mean (SD)	11.34 (2.27)		11.12 (2.01)			
Median (range)	11.4 (2–12)		11.6 (2–12)			
Duration of disease/years						
Mean (SD)	5.74 (3.45)		5.14 (3.20)			

Weight (Kg) Mean (SD	28 (7.65)		25 (6.67)			
Body mass index (BMI) kg/m2						
Mean (SD)	16.82 (8.73)		16.26 (6.78)			
Median (range)	16.5 (14–28)		16.9 (15–29)			
Family history of thalassemia major						
No	18	37.50	13	40.63	31	36.05
Yes	30	62.50	19	59.38	49	56.98
Family history of endocrine disorders						
No	30	62.5	19	59.38	49	61.25
Yes	18	37.5	13	40.63	31	38.75
Hemoglobin level before transfusion (Gram/DL)						
Mean (SD)	6.82 (1.45)		6.65 (1.89)			
Median (range)	7.5 (2.8–11)		7.2 (2.5–11)			
Splenectomy						
No	22	45.83	21	65.63	43	53.75
Yes	26	54.17	11	34.38	37	46.25
Deferasirox (N. of patients)	15	31.25	9	28.125	24	30
Desferoxamine (N. of patients)	10	20.83	7	21.875	17	21.25
Combined therapy (N. of patients)	23	47.92	16	50	39	48.75

Table 2: The prevalence of endocrine disorders of studied population

Characteristics	**Summary statistics Total 80 patients**				**Total**	
	Male		**Female**			
	N	**%**	**N**	**%**	**N**	**%**
No endocrine disorders	41	19.68	27	84.38	68	85.00
Impaired glucose tolerance (IGT)	1	0.48	1	3.13	2	2.50
Impaired fasting glucose (IFG)	1	0.48	1	3.13	2	2.50
Diabetes mellitus (DM)	0	0	0	0.00	0	0.00
Subclinical hypothyroidism	2	0.96	1	3.13	3	3.75
Clinical hypothyroidism	2	0.96	1	3.13	3	3.75
Hypoparathyroidism	1	0.48	1	3.13	2	2.50

Table 3: Risk factors of endocrine disorders in young children with thalassemia major

Characteristics	**Summary statistics Total 80 patients**				**Total**	
	Endocine Disorder 17(21.5%)		**No Endocine Disorder 63(78.75)**			
	N	**%**	**N**	**%**	**N**	**%**
Age mean (SD)	11.60 (3.21)		11.01 (1.27)			
Gender						

Female	5	29.41	27	17.01	32	40.00
Male	12	70.59	36	22.68	48	60.00
Malnutrition						
No	7	41.18	16	25.40	23	28.75
Yes	10	58.82	47	74.60	57	71.25
Splenectomy						
No	8	47.06	36	45.00	44	55.00
Yes	9	52.94	27	33.75	36	45.00
Family history of thalassemia major						
No	9	52.94	39	61.90	48	76.19
Yes	7	41.18	24	38.10	31	49.21
Family history of endocrine disorders						
No	10	58.82	35	55.56	45	56.25
Yes	7	41.18	28	44.44	35	43.75
Deferasirox						
No	9	52.94	41	65.08	50	62.5
Yes	7	41.18	22	34.92	29	36.25
Desferoxamine						
No	13	76.47	47	74.60	60	75.00
Yes	4	23.53	16	25.40	20	25.00
Combined therapy						
No	11	64.71	29	46.03	40	50.00
Yes	6	35.29	34	53.97	40	50.00

Table 4: Mean serum/blood levels.

Investigation	Mean levels
Serum TSH	2.9±1.4 IU/ml
Serum vitamin D3	22.2±2.7 ng/ml
Hba1c levels	4.7±1.1%
Serum calcium	8.5±1.3 mg/dl
Serum phosphate	4.2±0.7 mg/dl
Serum testosterone, (n=6)	0.75±0.18 ng/ml
Serum leutinizing hormone (LH), (n=8)	1.78±0.42 mIU/ml
Serum follicle-stimulating hormone (FSH), (n=8)	1.57±0.35 mIU/ml

DISCUSSION

Thalassemia major is the most common type of hemolytic anemia seen in Bangladesh. With availability of blood transfusion therapy and iron chelation therapy has increased the life expectancy of thalassemic child and more children are going from adolescent to the youth period with availability of a standardized and comprehensive treatment. But at the same time there is increase in various endocrinological complications in adolescent age group because of iron deposition in various endocrinological organs of the body. Mean pre-transfusion hemoglobin in our study is 7.6±1.1 gm/dL. Kumari V et al has also reported pre

transfusion Hb level of 7-10 gm/dl in 59.4% in their study. Most of the studies have documented pretransfusion Hb of 7-8 gm/dL which suggest that regular blood transfusion is needed to maintain a pretransfusion Hb of 9-10 gm/dl. Mean serum ferritin level in our study was 3179±788 ng/ml [18]. Despite of regular iron chelation therapy, serum ferritin level less than 1000 ng/dl was maintained in only 2% of the patients in our study group. Growth retardation is the most common complication observed in our study group. In present study, 35.41% of the children were undernourished and 27% of the children were stunted. The pathogenesis of growth failure in our study is multifactorial. The contributing factors for growth retardation in our patients with thalassemia major include chronic hypoxia due to anemic state, transfusion related iron overload, hypothyroidism, hypogonadism, growth hormone deficiency, undernutrition and psychosocial stress. In our study, being a government setup, we were not able to measure the growth hormone and IGF levels as these investigations are not done at our setup and patients were not able to afford this investigation due to monetary problem. Thus, we were not able to do growth hormone stimulation test, growth hormone level and IGF levels in each and every patient. In Chhabra et al study, out of 114 thalassaemic children of 8-16 years age group, they reported undernourishment in 78.1% and stunting in 56.1%.[8] The growth retardation is significantly lower in our group probably because of proper blood transfusion and proper chelation therapy. In our study, 2 females with thalassemia major have primary amenorrhea having low LH and FSH levels. Iron deposition in the pituitary gonadotrophic cells leads to disruption of gonadotropin (LH, FSH) production. Delayed puberty is found more commonly in females than males. Hypothyroidism was observed in 4 children (8.33%) in our study population. Patients in our study population were having a high TSH level with a low free T3 and free T4 level. The contributing factors for hypothyroidism in our study may be thyroid gland infiltration, anemia and chronic tissue hypoxia, free radical injury and organ siderosis. Vitamin D3 deficiency was present in 17 children (35.41%) and hypocalcemia was present in 13 children (27.08%) but serum phosphate and ALP levels were within normal limits which suggest hypocalcemia in our patients may be because of dietary insufficiency, however the PTH levels were not done in our centre because of lack of facility[19].Though the complications are mild in nature in our study, there is a significant increase in endocrinological complications observed when the serum ferritin level goes beyond 2500 ng/dL which suggest child with serum ferritin level beyond 2500 ng/dL should be treated and managed meticulously at tertiary care centre level so that the mean ferritin level can be lower down at early age with a combination of iron chelation therapy and other supportive treatment. Even though, if any complication occurs in a child with serum ferritin level less than 2500 ng/dl, prompt treatment can be started at appropriate time, so that further long-term complications can be prevented. In a large multicentric study of 3817 thalassaemic children from 29 countries, De Sanctis et al reported short stature in 31.1% male and 30.5% female. Similarly, Growth hormone deficiency was reported in 7.9% in males and 8.8% amongst females. Amongst the various Endocrine complications delayed puberty was in 40.5% (according to SMR staging) followed by hypothyroidism in 3.2%[20].

Limitations This study has a relatively small sample size and may limit the outcome of above interpretation. However, the outcome of this study will definitely encourage the future research work in this field.

CONCLUSION AND RECOMMENDATIONS

Growth retardation is the commonest endocrinological complication in children with

β thalassemia major. Though Endocrinological complications in adolescents were mild in severity in our study, they were observed when the serum ferritin went beyond 2500 ng/ml in children with β thalassemia major. Early identification and comprehensive multidisciplinary management specially for those children whose serum ferritin level are>2500 ng/ml are the key factor for prevention and treatment of thalassemic child with endocrinological complications.

Conflict of interest: None declared

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