Endocrine abnormalities in children with Beta thalassaemia major

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Abstract

Background: Endocrine complications in β-thalassaemia major patients in developing countries are likely to occur at younger ages due to suboptimal iron chelation.

Objective: To assess the prevalence of endocrine abnormalities and correlate serum ferritin, degree of anaemia and liver dysfunction with endocrine dysfunction

Method: A cross sectional study was carried out in B. J. Wadia Hospital, over a period of 2 years, on all children with β-thalassemia major over the age of 4 years receiving regular blood transfusions. Patients with transfusion dependent anaemia other than β-thalassemia major were excluded.

Results: The total number of children over 4 years of age with β-thalassaemia major receiving regular blood transfusions during the study period was 135. Mean haemoglobin was 7.8 ± 0.6g/dl and the mean serum ferritin level 5295 ± 2736ng/ml. The most common endocrine abnormality was delayed puberty (68%). Seventy one (52.5%) patients had short stature with the height Z-score 2.8±0.8. Hypocalcaemia was observed in 40 (38%) patients. Ten (9.4%) patients had hypoparathyroidism while in 7 (6.6%) it was suspected based on hypocalcaemia, high phosphorus and normal alkaline phosphatase. Rickets was seen in 25 (23.5%) patients. Hypothyroidism was present in 22 (22%) patients of whom 14 had compensated hypothyroidism. Insulin resistance, impaired fasting glucose/impaired glucose tolerance (IFG/IGT) and diabetes mellitus were seen in 7.6%, 4.4% and 2.6% patients respectively. Mean age of patients with delayed puberty was 15.8±1, short stature 10.3±3.4, hypoparathyroidism 10.4±4.2, hypothyroidism 10.4±3, IFG/IGT 10.4±2 and diabetes mellitus 14.2±1.2 years. Bone mineral density was done in 48 patients older than 10 years. Eighteen (37.5%) patients had spinal osteoporosis. Five patients had more than one endocrine abnormality.

Conclusions: There were no statistically significant differences between the patients with and without endocrine abnormalities with respect to serum ferritin, mean pre-transfusion haemoglobin and liver dysfunction except for ferritin in patients with hypoparathyroidism and diabetes mellitus.

(Key words: β-thalassaemia; serum ferritin; endocrine; haemoglobin; transaminase)

Introduction

Iron overload and deposition of iron in vital organs due to repeated transfusions and inadequate chelation therapy causes morbidity in patients with β-thalassaemia major. Iron deposition involves the hypothalamic pituitary axis and endocrine glands. Most of the endocrine abnormalities reported from developed countries are after 10 years of age[1,2]. However, in developing countries, there is the possibility of having a high prevalence of endocrine complications at an early age due to suboptimal transfusions and chelation. We present the endocrine evaluation in a group of children with thalassaemia, managed at B. J. Wadia Hospital for Children, Mumbai.

Objective

To assess the prevalence of endocrine abnormalities and correlate serum ferritin, degree of anaemia and liver dysfunction (transaminase levels) with endocrine dysfunction

Material and methods

A cross sectional study was carried out in B. J. Wadia Hospital over a period of 2 years from 1st January 2007 to 31st December 2009.on on all children with β-thalassemia major over the age of 4 years receiving regular blood transfusions. Patients with transfusion dependent anaemia other than β-thalassemia major were excluded from the study.

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Anthropometry and investigations which were part of routine care like haemoglobin (Hb), serum ferritin and alanine transaminase (ALT) were done. Pre-transfusion Hb was calculated as mean of all the readings over the two years. A thorough history was taken and examination performed to look for clinical features of glucose intolerance, hypoparathyroidism, rickets and hypothyroidism. Height was plotted on national growth charts and also expressed as standard deviation (z) scores against Indian reference data[3]. Bone age was evaluated according to Greulich and Pyle method and puberty was evaluated according to Tanner's classification.

All patients were advised endocrine evaluation. However, all did not consent to undergo every test. Thus 100 patients underwent thyroid function tests (T3, T4, TSH), 52 patients underwent oral glucose tolerance test (OGTT) test and an additional 61 only fasting plasma glucose. Eight patients with delayed puberty underwent estimation of gonadal steroids (testosterone/estradiol) with gonadotropins (FSH, LH) and 106 patients underwent testing for calcium status [serum calcium (Ca), phosphorus (P), alkaline phosphatase (AP)]. Hypocalcaemic (serum Ca <8.5 mg/dl) patients were further evaluated by doing serum iPTH, 25-hydroxy vitamin D [25(OH)D] level/ x-ray wrist as necessary. Oral glucose tolerance test (OGTT) was performed with a 1.75g/kg (max. 75 g) oral glucose load. Values were interpreted by WHO criteria[4]. Impaired fasting glucose (IFG) was diagnosed if fasting plasma glucose was >110mg/dl and <126 mg/dl. Impaired glucose tolerance (IGT) was diagnosed if the 2 hour post oral glucose plasma glucose was >140 mg/dl and <200 mg/dl. Diabetes was diagnosed if the fasting plasma glucose was >126 mg/dl and 2 hours post oral glucose/any random plasma glucose was >200 mg/dl. Non-diabetic patients underwent evaluation of insulin resistance (IR) index using the homeostasis model assessment (HOMA)[5]. IR index value of >3.4 was taken as indicative of insulin resistance.

Bone mineral density (BMD) was evaluated in 48 children (23M, 25F) above 10 years by doing Dual Energy X-ray Absorptiometry (DEXA) using GE Medical Systems Lunar Prodigy device. BMD was done by one radiologist on whole body and at lumbar spine (L1-L4). Results were expressed as gram per square centimetre. Z-scores were calculated based on BMD of normal age and sex-matched Caucasian population provided by the manufacturer of the DXA device. Z score between -1.5 and -2.5 SD was considered osteopenia whereas below -2.5 SD as osteoporosis[2].

Data were analysed using statistical package for social sciences (SPSS) software. Numerical data are presented as mean ± SD or median. A p value<0.05 was regarded as significant.

Results

Of the 135 patients with β-thalassemia major on regular transfusion therapy, 72 were males. Ages ranged from 4 to 18 years with a mean age of 10.1±3.4 years. There were 55 patients (31M, 24F) below10 years of age and 80 patients (41M, 39F) 10 years or more. Desferrioxamine or deferiprone was advised in all patients. However, most of the patients took irregular chelation and that too in improper doses (taking when they could afford or taking whatever minimal they could afford) citing financial reasons.

Mean pre-transfusion Hb, mean serum ferritin, mean serum ALT and height Z scores observed over the 2 years of study are shown in Table I.

Table 1: ***Patient characteristics (n=135)***

Characteristic	Value (mean ±SD)
Pre-transfusion hemoglobin (g/dl)	7.8 ± 0.6
Serum ferritin (normal15-300ng/ml)	5295 ± 2736
Serum ALT (N-0-40U/l)	95±22
Height Z score	
Whole group (n=135)	-2 ± 1.1
Patients with short stature (n=71, 52.5%)	-2.8 ± 0.8
Patients with normal stature (n=64, 47.5%)	-1.1 ± 0.4

ALT- alanine aminotransferase; Z score- standard deviation score against national references

Of the 135 patients, 130 (96%) had mean Hb <9g%, 116 (86%) had serum ferritin levels >2500ng/ml and 64 (47%) >5000ng/ml. None had serum ferritin <1000ng/ml whilst 19 (14%) had serum ferritin levels between 1000-2500ng/ml. The mean age, mean serum ferritin level and mean haemoglobin levels in patients with endocrine abnormalities are shown in Table 2.

Table 2: ***Mean age, mean serum ferritin and mean Hb levels in patients with endocrine abnormalities***

Endocrine abnormalities	Age*(years)	Ferritin*(ng/ml)	Hb*(g/dl)
Short stature (n=71)	10.3±3.4	5359±2791 [0.65]	7.7±0.5 [0.22]
Delayed puberty(n=17)	15.8±1	5880±4125 [0.18]	8.1±1.1 [0.8]
Hypoparathyroidism(n=17)	10.4±4.2	7205±3707 [0.02]	7.8±0.9 [0.6]
Hypothyroidism(n=22)	10.4±3	5763± 2543 [0.52]	7.7±0.7 [0.45]
IR(n=4)	12†	3758±653 [0.24]	7.7±0.2 [0.19]
IFG/IGT(n=5)	10.9†	5485±1200 [0.58]	7.6±1.9 [0.63]
DM(n=3)	14.2†	12533±1245 [0.0007]	8.7±0.7 [0.67]

** Mean ± SD; † median; Numbers in [ ] indicate p values*

The prevalence of endocrine abnormalities in children less than 10 years of age and in children 10 or more years of age is shown in Table 3.

Table 3: ***Prevalence of endocrine abnormalities in thalassaemic patients***

Endocrine abnormality	<10years No. (%)	≥10 years No. (%)
Short stature	22/55 (31)	49/80(69)
Delayed puberty	-	17/25(68)
Hypocalcaemia	18/43 (41)	22/63(35)
Hypoparathyroidism -proven -suspected	 2/43 (4.6) 2/43 (4.6)	 8/63(12.6) 5/63(8)
Rickets	10/43 (23)	15/63(24)
Hypothyroidism	8/39 (21)	14/61(23)
IR	-	4/52(7.6)
IFG/IGT	2/48 (4)	3/65(4.6))
DM	-	3/113(2.6)

Stature and Puberty: Seventy one (52.5%) patients (32M, 39F) had short stature. Twenty two patients (12M, 10F) were less than 10 years with a mean age 7.2±1.8 years and mean Z score -2.7±1.1 while 49 patients (20M, 29F) were 10 years or older with a mean Z score of -2.9±0.6. Twenty two of these patients had hypothyroidism and 17 had delayed puberty. Mean ferritin level was higher than in children with normal stature (5124±2685ng/ml). Raised ALT was present in 54% patients. Mean Hb was <9 g/dl in 70 patients. Delayed puberty was seen in 9 male and 8 female thalassaemic patients. 40% of these patients had raised ALT. Patients (n=8) evaluated for delayed puberty had hypogonadotropic hypogonadism (pre-pubertal FSH, LH and testosterone/estradiol levels).

Thyroid, calcium and glucose tolerance: Eight (5M, 3F) patients having primary hypothyroidism were below 10 years with a mean age of 6.9±1.3 years (youngest patient 4.5 years). Fourteen patients (7M, 7F) were older than 10 years with a mean age of 12.4±1.8yrs. ALT was raised in 47% patients. Fourteen patients (n=7, <10years and ≥10 years) had compensated hypothyroidism (normal T3, T4, elevated TSH). Remaining 8 patients presenting with features like constipation, reduced activity and decreased school performance had low T4 and elevated TSH. Seven of these patients had significantly delayed bone age (delay of more than two years from the chronological age).

All patients with diabetes presented with polyuria and polydipsia without ketoacidosis. They had low c-peptide levels and required high insulin dose (1.7-2 u/kg/d) for achieving good glycaemic control. ALT was raised in one patient (25%) with IR, 2 patients (66%) with IFG/IGT and all patients with diabetes mellitus.

Hypocalcaemia was observed in 40 patients (37.7%). Hypoparathyroidism (low/low normal iPTH levels in presence of hypocalcaemia) was seen in 9.4% patients while it was strongly suspected in 7 patients (6.6%) based on low Ca, significantly raised serum P (>8.5 mg/dl) and normal AP. Serum Ca ranged from 6.9-8.3 mg/dl. ALT was increased in 50% patients. Only 3 patients had mild symptoms in form of paraesthesiae in hands and feet. Rickets was seen in 25 patients (23.5%). Six of them had low 25(OH) D levels (<10ng/ml). Eighteen patients were diagnosed on basis of normal/decreased serum phosphorus, increased alkaline phosphatase (range 640-1050 IU/L) and X-ray wrist showing metaphyseal cupping, splaying and fraying.

Bone mineral density: Total body BMD revealed osteoporosis in 7 (14.5%) and osteopenia in 20 (41.6%) patients. Spinal osteoporosis was seen in 18 (37.5%) and osteopenia in 12 (25%) patients. Mean Z score BMD in patients with delayed puberty (S: -2 ±0.5; TB: -1.3±0.06) was lower than other patients (S:-1.33±0.6; TB: -1.1±0.2). 9 patients with hypocalcaemia and 18 with short stature also had low BMD. Increased ALT was present in 42% patients. Mean ferritin and Hb was 6033±3575ng/ml and 7.6±0.5 g/dl respectively in these patients with low BMD.

Five patients had more than one endocrine abnormality: Diabetes mellitus, hypothyroidism, vitamin D deficiency, hypoparathyroidism and delayed puberty all present in one patient, hypothyroidism and hypoparathyroidism in 2 patients, diabetes mellitus and hypoparathyroidism in 1 patient and IGT and hypothyroidism in 1 patient. There was no significant statistical difference between the patients with and without endocrine abnormalities with respect to serum ferritin, mean pre-transfusion Hb and ALT except for significant correlation of serum ferritin in patients with hypoparathyroidism and diabetes mellitus ($p<0.05$).

Discussion

Chronic anaemia, hypoxia and iron overload are considered to be responsible for secondary endocrine dysfunction in patients with thalassaemia[6]. Delayed puberty was the most common endocrine abnormality (68%) seen in our study. Eight patients evaluated had failure of pituitary gonadal axis (hypogonadotropic hypogonadism) which is a common cause of delayed/ arrested puberty due to sensitivity of anterior pituitary to iron toxicity[6]. Similar findings were observed by Najafipour et al from Iran[7] (impaired puberty in 71%) and in a multicentre study by Thalassemia International Federation (TIF, lack of pubertal changes in 40.5% patients)[8]. Short stature was the next common abnormality seen in our study, which is similar to the prevalence of 30-70% reported in literature[7-10]. Short stature and hypogonadism are common in patients with ferritin levels more than 2000µg/l[10]. Deposition of iron causes glandular damage due to free radical formation and lipid peroxidation causing mitochondrial, lysosomal and sarcolemmal membrane damage[11]. Therefore, it seems logical to consider that patients with high ferritin levels are more likely to develop endocrine complications, a feature seen in our patients with endocrine dysfunction (mean ferritin >5000ng/ml in most patients). However, our study showed no statistical correlation between stature and ferritin levels. The reason could be that aetiology of growth failure in thalassaemia is multifactorial like chronic disease, hypoxia, deranged liver functions, decreased IGF-1 activity, impaired growth hormone secretion as well as its neurosecretory dysfunction.

Hypoparathyroidism is reported in 3.6-22.5% patients with thalassaemia major[8,9,11]. Majority of patients are asymptomatic while a few have mild symptoms[11], as seen in our patients. Rickets was seen in 23.5% of our patients. Vitamin D deficiency was seen in 100% patients by Soliman et al [12], in 37.2% patients by Shamsiraz et al [9] while 12% patients were deficient and 70% insufficient in a study done in North America[13]. Vitamin D deficiency has been attributed to defective 25-hydroxylation in the liver[1], malabsorption of vitamin D as well as inadequate nutrient intake[6,9].

Thyroid dysfunction is reported in 3-27% patients with thalassaemia, but its severity is variable as seen in different series[7-9,14,15]. As opposed to the gonadal axis, thyroid gland appears to fail before the central components of pituitary-thyroid axis. Moreover, most studies report a high prevalence of subclinical primary hypothyroidism. Both these features were seen in our study with 14 patients having no clinical features of hypothyroidism. Abnormal glucose tolerance is common in multi-transfused patients attributed to early impaired β-cell function and increasing insulin resistance (IR) with age[16,17]. Impaired carbohydrate metabolism was seen in 14.6% of our patients, quite similar to a study from Thailand where the prevalence was 12.5% in patients receiving hypertransfusion with sub-optimal iron chelation (ferritin level 8679±4710µg/L)[18]. A study has shown that diabetes risk is reduced below serum ferritin of less than 2500µg/L[19]. Intensive chelation with a combination of desferrioxamine and deferiprone is known to improve glucose metabolism disorders in thalassaemia major patients[20] .Hepatic dysfunction may be important cause for development of IR and abnormal glucose tolerance [19], a feature seen as deranged ALT in 25% and 66% of our patients with IR and IGT.

Low bone mass (LBM) has been reported in 40-60% of patients with β-thalassaemia[6]. Expansion of bone marrow spaces may contribute to osteopenia/ osteoporosis. The lumbar spine which is exclusively trabecular bone and consists of wide bone marrow spaces is the most affected part[21]. Osteopenia in suboptimally transfused thalassaemics with iron overload is primarily caused by focal osteomalacia and decreased bone formation with partial contribution from iron deposits in bone and low circulating IGF-1[21]. Other factors contributing to LBM include delayed puberty, multiendocrine dysfunction, vitamin D deficiency and hypoparathyroidism.

Endocrine evaluation in patients with thalassaemia has been recommended after 10 years[1,2], at age of 12 years for thyroid dysfunction, at puberty for impaired carbohydrate metabolism and at 16 years for hypoparathyroidism by TIF. Endocrine complications were observed at a younger age in our study as compared to other studies[7,9]. While growth failure is commonly seen in children above 10 years of age[2,22],

31% of our patients below 10 years were short. In studies done by Shamsiraz[9] and Najafipour[7] mean age of patients with hypothyroidism was 16.4±4.1 and 17.3±4.2 years; diabetes was 15±3 and 19.8 ±4.3 years and hypoparathyroidism/hypocalcaemia was 16.9±3.7 and 14.5±3.2 years respectively as compared to earlier age in our patients. It is possible that early appearance of endocrine abnormalities is related to the poor chelation status of our patients. Though a correlation between ferritin and endocrine dysfunction was not found (except for hypoparathyroidism and diabetes), there may be reasons for this. Ferritin measured during a year or two may not be representative of the ferritin maintained by the patient during the whole of childhood. Moreover, it is possible that endocrine dysfunction occurs at relatively lower levels of tissue iron[23], there may be individual sensitivity to iron damage and other mechanisms like increased collagen deposition secondary to increased activity of the iron-dependent protocollagen proline hydroxylase enzyme, with subsequent disturbed microcirculation in the endocrine glands[24] may operate. Iron overload can be tackled by involvement of government and NGOs as all the iron chelators are available and even the pharmaceutical companies have assistance programmes. This would help in the future to avoid the irreversible consequences of iron overload.

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