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The Endocrine Dysfunction in Multitransfused Thalassemic Patients

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Abstract

Background: Every year 10,000 children with thalassemia major are born in India, which constitutes 10% of the total numbers in the world. The current management of thalassemia major (TM) includes regular transfusion programs and chelation therapy. The combination of transfusion and chelation therapy has dramatically extended the life expectancy of thalassaemic patients but is complicated by citrate toxicity and subsequent iron overload. Excessive iron is deposited in most tissues primarily in the liver, heart and the endocrine glands Disorders of growth, sexual development & fertility, abnormal bone mineralisation, diabetes mellitus, hypothyroidism and hypoadrenalism are the main endocrine complications found in thalassaemic patients. *Aims And Objectives:* To determine the incidence of thyroid dysfunction by estimating T3, T4 and TSH, hypoparathyroidism by estimating serum calcium, phosphorus and alkaline phosphatase levels,diabetes mellitus by estimating fasting and post-prandial blood suger, to see for pubertal delay in these patients according to sexual maturity rating and finally to determine if there is any co-relation between increased serum ferritin and these abnormalities. *Material and Methods:* This study was conducted in the department of Paediatrics, Thalassemia Unit, Government Medical College , Jammu. All thalassemic children below the age of 19 years who had received more than 20 transfusions and whose ferritin levels were more than 1000mg/ng and were coming regularly for transfusion in the thalassemia unit of department of paediatrics were included in the study. *Results:* The height and weight of these children were significantly less (>2.5 SD) as compared to normal children. Hypothyroidism was detected in 12.82% of the patients,hypocalcemia was detected in 20 cases, hypoparathyroidism in 8 patients, impaired glucose tolerance was detected in 25.7%, *Conclusion*: Increasing awareness of endocrinological problems in thalassemic patients is essential not only because such patients are living longer now, but also because much of the morbidity and mortality from these complications can be reduced with regular surveillance, early treatment and follow-up .

Keywords: Thalassemia Major; Blood Transfusion; Serum Ferritin; Delayed Growth; Puberty; Hyopothyroidism; Hypoparathyroidism; Diabetes.

Introduction

The hemoglobinopathies (thalassemias and sickle-cell disease) are the most commonly inherited genetic disorders [1] and according to figures available with World Health Organisation, 5% of the world population is a carrier for hemoglobinopathies and out of these, thalassemia syndromes, particularly beta thalassemia major is serious and a major cause of morbidity [2]. The frequency of β-thalassemia in India ranges from 3.5% to 15%, in general, population [3]. Every year 10,000 children with thalassemia major are born in India, which constitutes 10% of the total numbers in the world [4].

Thalassaemia major is a hereditary disorder of haemoglobin synthesis and the homozygous state results in severe anaemia. Historically the homozygous condition was known to affect a

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significant population in Mediterranean countries and the Middle East; however, migration has changed the geographic spread and made it a worldwide health problem. The current management of thalassemia major (TM) includes regular transfusion programs and chelation therapy. Current guidelines recommend a pre-transfusion threshold not exceeding 9.5% g/dl, which seems to be associated with adequate marrow inhibition and a relatively low iron burden. The aim is to transfuse 10-20 ml/kg body weight of packed filtered red cells over a period of 2-3 h every 2 to 5 weeks throughout life [5]. The combination of transfusion and chelation therapy has dramatically extended the life expectancy of thalassaemic patients but is complicated by citrate toxicity and subsequent iron overload resulting in a high incidence of endocrine abnormalities in children, adolescents and young adults [6,7,8].

The precise underlying mechanism of iron overload-induced organ dysfunction presently remains unclear. However, when iron levels in the body become too high, this leads to saturation of transferrin, and non-transferrin-bound iron (NTBI) species circulate in the plasma. Unbound iron within cells or in plasma is labile and can redox cycle between Fe^{2+} and Fe^{3+}, thereby generating reactive oxygen species (ROS), leading to lipid peroxidation. Lipid peroxidation under conditions of iron overload leads to the generation of both unsaturated (malondialdehyde and hydroxynonenal) and saturated (hexanal) aldehydes. Both have been implicated in cellular dysfunction, cytotoxicity, and cell death [9,10.11].

Apart from iron overload, other factors responsible for organ damage have been previously pointed out, including chronic hypoxia due to anemia that may potentiate the toxicity of iron deposition in endocrine glands. Also, viral infections as well as individual susceptibility have been implicated in causing endocrine dysfunction [12]. NTBI is also a catalyst for the formation of reactive oxygen species, causing oxidative damage [13]. Certain tissues are particularly susceptible to excess iron incorporation when NTBI is present e.g the anterior pituitary gland , in a dose-dependent fashion, is particularly sensitive to the effects of iron overload from transfusions [14].

Excessive iron is deposited in most tissues primarily in the liver, heart and the endocrine glands disorders of growth, sexual development & fertility, abnormal bone mineralisation, diabetes mellitus, hypothyroidism and hypoadrenalism are the main endocrine complications found in thalassaemic patients [15-19].

Aims and Objectives

To determine the incidence of —

Thyroid dysfunction by estimating T3, T4 and TSH

Hypoparathyroidism by estimating serum calcium, phosphorus and alkaline phosphatase

Diabetes mellitus by estimating fasting and post-prandial blood suger pubertal delay in these patients according to sexual maturity rating, and finally to determine if any co-relation exists between increased serum ferritin and these abnormalities

Material and Methods

This study was conducted in the department of Paediatrics, Thalassemia Unit, Government Medical College, Jammu, for a period of one year. The 39 multitransfused thalassemic children between 2—21 years of age, who had received more than 20 transfusions and whose ferritin levels were more than 1000mg/ng and were coming regularly for transfusion in the thalassemia unit of department of paediatrics were included in the study after obtaining informed consent from the parents. The diagnosis of thalassemia was established by the following criteria

- Profound hypochromic anaemia with severe red cell dysplasia and erythroblastosis in blood smears
- Raised levels of HbF
- Confirmation of thalassemic traits in both parents

Multitransfused state was levelled for patients who had received >20 transfusion at the time of enrollment. All the participants of the study were subjected to complete physical examination and various investigations including the following blood tests –

- Serum ferritin by elisa
- Thyroid function tests by radioimmuoassay
- Serum calcium by calorimeter methods
- Phosphorus by photometric UV test

Alkaline phosphatase by Kind and King's method

Glucose tolerance test

Puberty was scaled according to sexual maturity rating scale developed by Tanner

Observations and Results

69% of patients were below 10 years whereas 31%

were above 10 years of age.

The youngest patient was 3 year old and oldest 21 years old. Table 1 Sex distribution of thalassemic patients. Males are more number constituting 69% of total patients.

The height and weight of these children were significantly less (>2.5 SD) as compared to normal children. The development of secondary sexual characteristics was significantly delayed in all 11 children. Hypothyroidism was detected in 12.82% of the patients and aymptomatic hypocalcemia was detected in 20 cases, out of which 8 patients were suffering from hypoparathyroidism. Impaired glucose tolerance was detected in 25.7% patients with no case of overt diabetes seen in group.Serum ferritin was increased in all 39 patients, however there was no statistically significant co-relationship between mean serum ferritin levels of children with hypothyroidism, hypoparathyroidism and impaired GTT with those of normal subjects .

Table 1: Sex distribution of thalassemic patients

Sex	No. of patients	Percentage
Males	27	69%
Females	12	31%

Table 2: Age distribution of thalassemic patients

Age group	No. of patients	Percentage
1-5	9	23.07%
6-10	18	46.13%
11-15	8	20.50%
>15	4	10.25%

Discussion

Aithough Endocrinopathies are amongst the common complications of thalassaemia (85.7% of patients were suffering from endocrine disorders in one study, the most common endocrine abnormality was hypogonadism in 71.4% of multitransfused children followed by hypoparathyroidism, diabetes and hypothyroidism with values of 21.4%, 14.3% and 7.2% respectively [19]) but determining the exact prevalence is difficult because of differences in age of first exposure to chelation therapy and the continuing improvement in survival in well-chelated patients. Bannerman et al. in 1967 published the first report of multiple endocrinopathies [20] in multitransfused children. Disorders of growth, sexual development & fertility, abnormal bone mineralisation, diabetes mellitus, hypothyroidism and hypoadrenalism are the main endocrine complications found in thalassaemic patients.

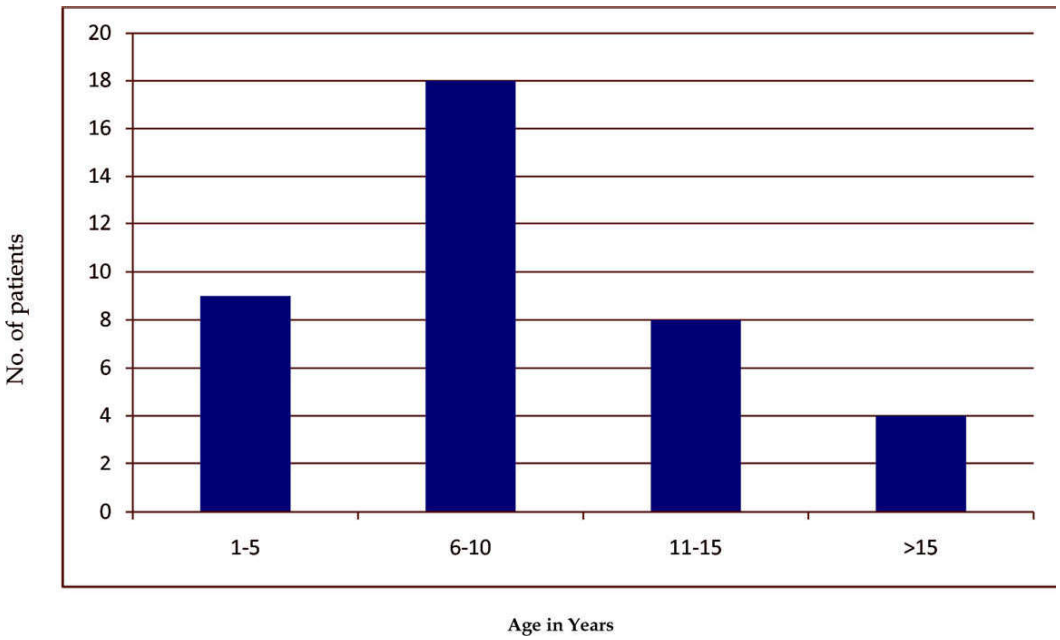

Fig. 1: Bar Chart depicting the age distribution of Thalassemic patients

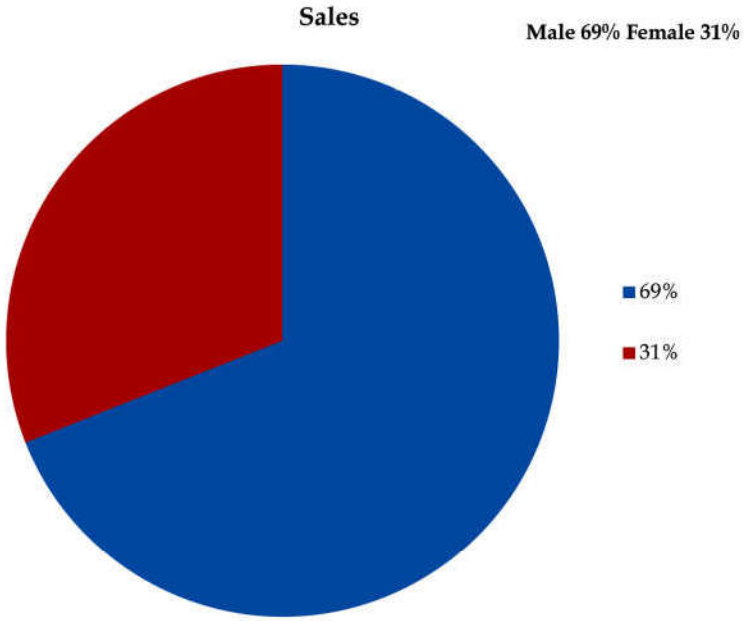

Fig. 2: Pie Chart depicting sex distribution of thalassemic patients

Table 3: General Physical Examination in thalassemic patients

Clinical Parameter	No of Patients	Percentage
Pallor	39	100
Change in skin colour (hemosiderosis)	20	51.2
Hepatomegaly	37	94.8
Splenomegaly	33	84.6

Pallor was present in 100% patients. More than half of the patients (51.2%) had clinical evidence of hemosiderosis as manifested by chances in skin colour. 94.8% & 84.6% had hepatomegaly & Splenomegaly respectively.

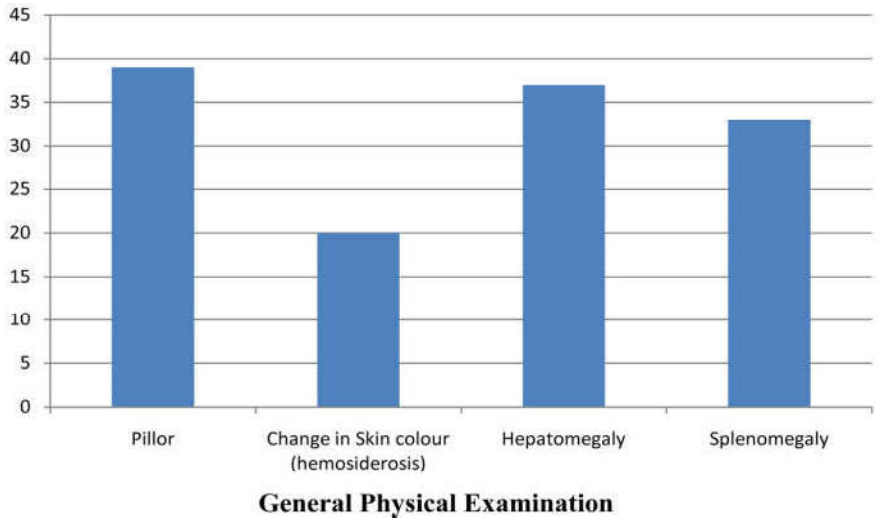

Fig. 3: Bar chart depicing general physical examination in thalassemic patients

Table 4: Hepatic enlargement in thalassemic patients

Liver size (cm BRCM)	No. of patients	Percentages
2-4	20	54.05%
4-6	12	32.4%
6-8	5	13.6%

54.05% patients had hepatic enlargement upto 4 cms, whereas 32.4% had hepatomegaly 6 cms & in 13.6%, there was huge liver enlargement utpo 8 cms.

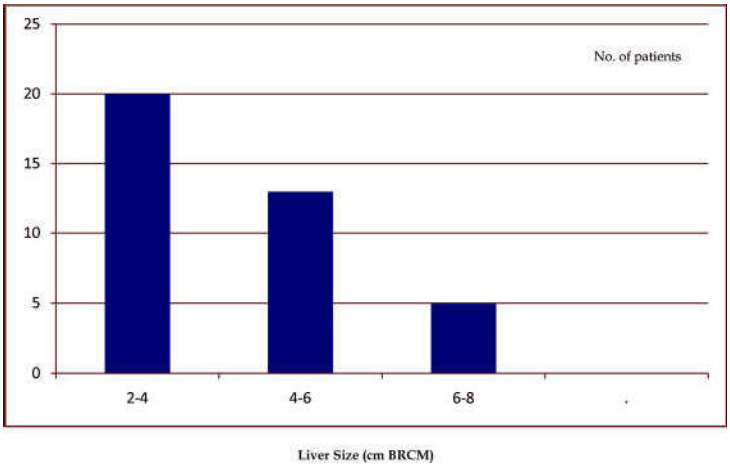

Fig. 4: Bar chart depicting Hepatic enlargement in thalassemic patients

Table 5: Splenic enlargement in thalassemic patients

Spleen size	No. of Patients	Percentage
2-4	14	42.4%
4-6	10	30.%
6-8	5	15.1%
8-10	4	12.2%

33 patients had Splenomegaly. 42.4% had splenic enlargement of 2-4 cm & 12.2% had massive Splenomegaly upto 8-10 cms. Three patients had undergone splenectomy

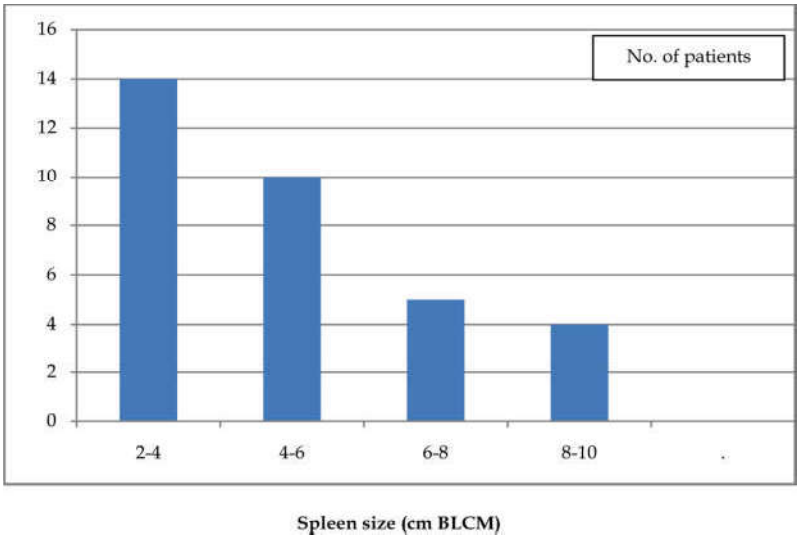

Fig. 5: Bar Chart depicting splenic enlargement in thalassemic patients

Table 6: Anthropmetric relation of thalassemics with normal values

Age Group (years)	No. of Patients	Height (cms)		Weight	
		Thalassmics (mean)	Normal (Mean)	Thalassemiscc (mean)	Normal (mean)
2-5	9	91.3	91	13.60	13.84
6-10	18	117.6	120	20.3	25.8
11-15	8	129.5	145	26	43.24
>15	4	157	160.3	47.25	51

There was no statistical difference in height and weight between thalassemics and normal children below 10 years of age, whereas significant difference was observed in age group 11-15 years(Z= > 2.5SD). No statistical significant difference in height and weight was observed in age group more than 15 years as the number of patients in this group is very small (eg.4).

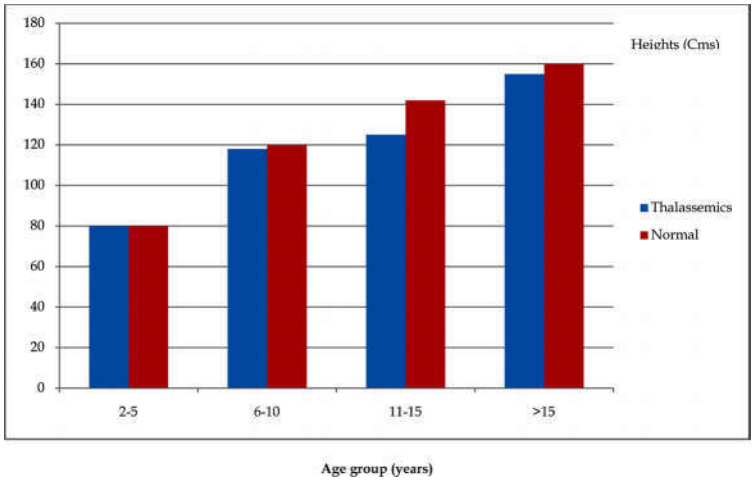

Fig. 6: Bar Chart depicting anthropometric relation of thalassemics with normal values

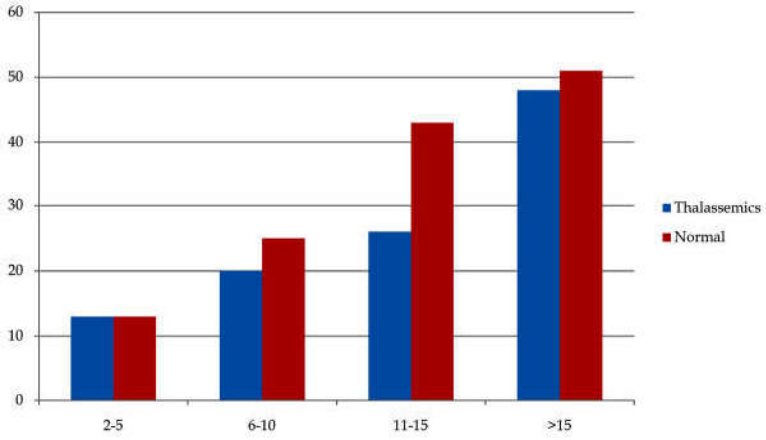

Table 7: Blood Transfusion received by thalassemics patients

Blood Transfusions	No. of Patients	Percentage
20-50	10	25.64%
50-100	12	30.73%
100-200	10	25.64%
>200	7	17.94%

Minimum number of blood transfusion received by a patient was 24 and maximum number of transfusions received was 320. 56.4% patients had less than 100 transfusions & rest had more than 100 blood transfusions.

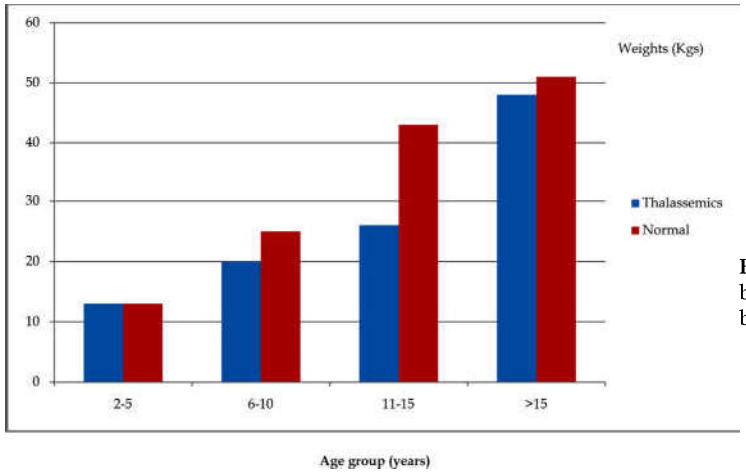

Fig. 7: Bar Chart depicting blood transfusions received by thalassemics patients

Table 8: Serum ferritin level in thalassemic patients

Serum Ferritin (ng/ml)	No. of Patients	Percentage
1000-2000	15	38.46
2001-4000	18	46.15
4001-6000	5	12.8
6001-8000	1	2.56

84.61% patients had serum ferritin levels than 4000 ng/dl and 1 patient has serum ferritin level more than 6000 ng/dl.

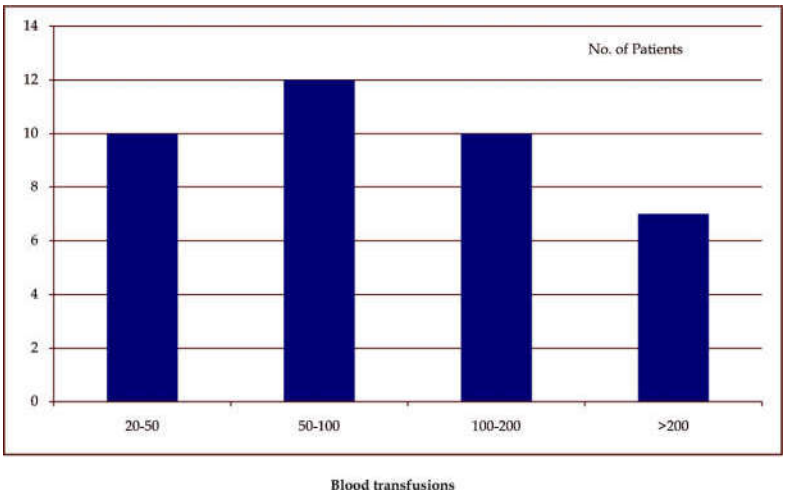

Fig. 8: Bar Chart depicting Serum Ferritin levels in thalassemic Children

Table 9: Relationship between number of blood transfusions and serum ferritin levels

S. No	Total no. of Blood Transfusions	Serum Ferritin (mean)
1	20-50 (n=10)	1504.8
2	50-100 (n=12)	2391.71
3	100-200 (n=10)	3523.2
4	>200 (n=7)	3674.57

Serum ferritin showed an increase with increase in number of blood transfusions. After 50 blood transfusions, no significant difference in serum ferritin was found as most of the patients were receiving chelation therapy by then.

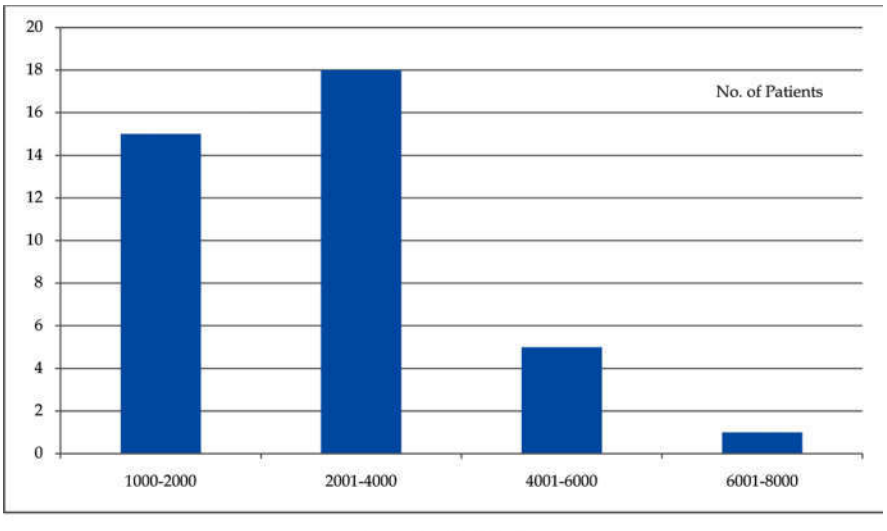

Fig. 9: Bar Char depicting relation between number blood transfusions & serum ferritin levels

Table 10: Sexual Maturity rating of male adolescent thalassemic children (n=4)

S. No.	Age	SMR Stage (Expected)	Serum Ferritin
1	17	2 (5)	3100
2	21	3 (5)	4880
3	15	2 (4)	2500
4	12	1 (2)	2900

Table 11: Sexual Maturity rating of female adolescent thalassemic children (n=7)

S. No.	Age	SMR Stage (Expected)	Serum ferritin
1	13	2 (3)	3550
2	16	2 (4)	4992
3	19	4 (5)	3550
4	13	2 (3)	3550
5	10	1 (2)	3890
6	13	2 (3)	2100
7	13	2 (3)	1010

All the 11 adolescent patients (4 Males & 7 Females) had delayed puberty

Table 12: Result of thyroid function test in thalassemic children

S. No.	Thyroid Status	No. of patients	Percentage
1	Euthyroid	34	87.18
2	Compensated hypothyroid	4	10.25
3	Decompensated	1	2.56

Hypothyroidism was found in five cases (12.81%) out of 39 Cases. 4 had compensated hypothyroidism (normal T4; raised TSH) and 1patient had decompensated hypothyroidism (decreased T4; raised TSH)

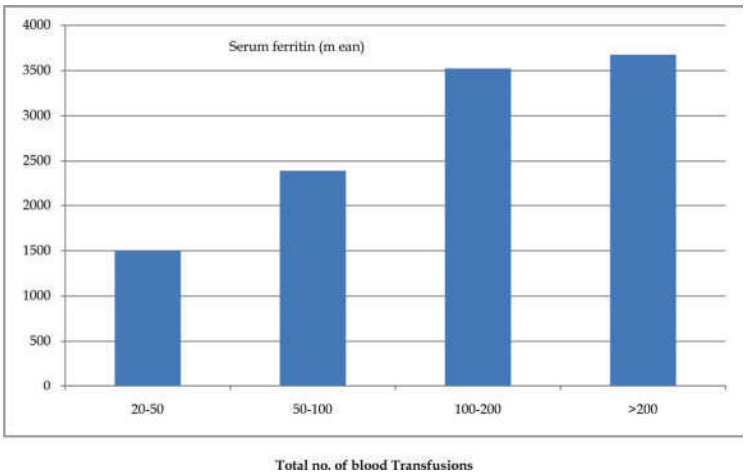

Fig. 10: Bar Chart depicting results of Thyroid functions in Thalassemic children

Table 13: Relationship between mean serum ferritn and children with hypothyroidism

S. No.	Thyroid status	No. of Patients	Serum Ferritin
1	Hypothyroid	5	3548
2	Euthyroid	34	2465.79

No statically significant difference (P value >0.05) in mean serum ferritin levels were found between patients with hypothyroidism and those with normal thyroid status.

Table 14:

S. No.	Calcium Status	No. of pts	Percentage
1	Normal	19	48.7
2	Isolated Hypocalcemia	12	30.8
3	Associated with Increased PO4 (Hypoparathyroidism)	8	20.5

51.3% patients had hypocalcemia. 30.8% had isolated hypocalcemia and 20.5% had hypocalemia associated with increased PO4, levels (i.e. hypoparathyroidism)

Table 15: Parathyroid status of thalassemic children

S. No.	Parathyroid status	No. of patients	Percentage
1	Normal	31	79.48
2	Hypoparathyroid	8	20.52

8 cases (20.52%) out of 39 were found to be hypoparathyroid. None was clinically symptomatic.

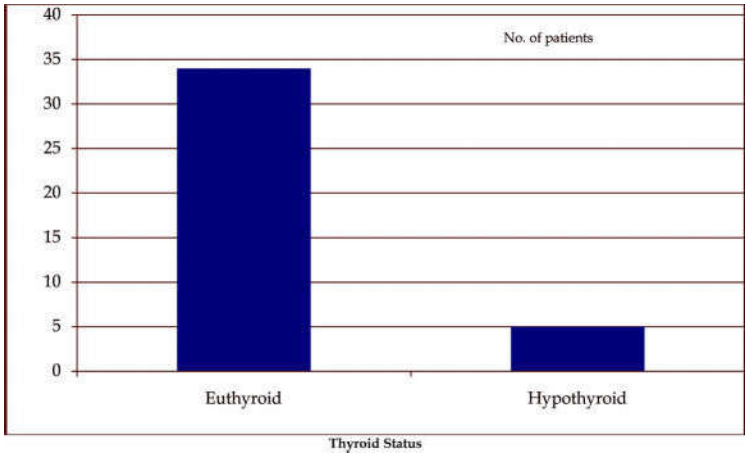

Fig. 11: Bar Chart depicting parathyroid status of thalassemic children

Table 16: Relation between serum ferritin and parathyroid status

S. No.	Parathyroid status	No. of patients	Mean serum ferritin
1	Normal	31	2836.25
2	Hypoparathyroid	8	2227.37

No statistically significant difference (P value >0.05) in mean serum ferritin levels was found between patients with hypoparathyroidism and those with normal pararthyroid status.

Table 17: Glucose Tolerance test in thalassemic children

S. No	GTT Status	No. of patients	Percentage
1	Normal	29	74.3
2	Impaired GTT	10	25.7
3	Diabetic	-	-

10 (25.7%) out of 39 patients had impaired glucose tolerance test. None of the patients had diabetes

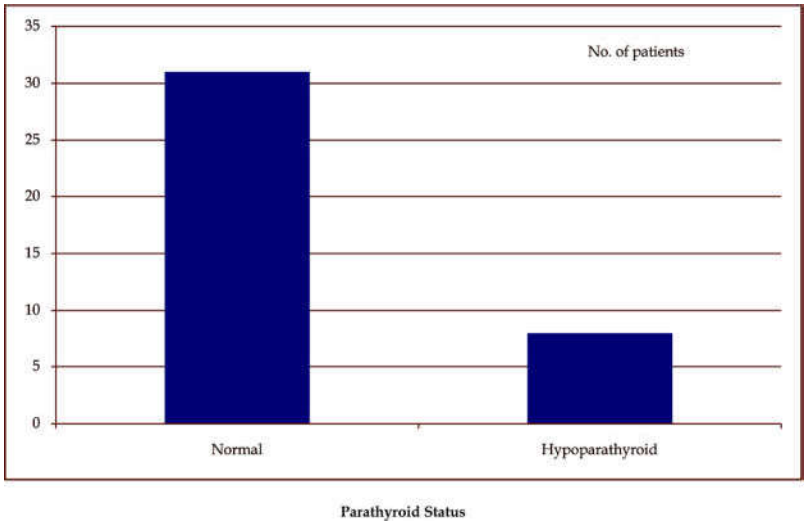

Fig. 12: Bar chart depicting results of Glucose Tolerance Test in Thalassemic children

There were 27 males and 12 females in the study group. Mean age of the patients in the study was 8.8 years and 57% of children were in the age group 6-15 years. The anaemia was mild in 2.5% of the patients, moderate (HB 7-10 gm/dl)in 87% and severe (Hb < 7) in 10.5% of the participants. The 51.2% patients exhibited skin changes because of iron overload, although these patients were on chelation therapy.

Anthropometric measurements in the form of height and weight were analysed in all 39 cases and were compared with normal values for the corresponding ages. In children less than 10 years, there was no difference in mean for height and weight between thalassemic and normal children where as significant decrease in height and weight was observed in age group 11-15 years. The thalassaemic children show retardation of growth in the foetal, infantile, the pre-pubertal and the pubertal periods. Approximately 20%- 30% of such patients have growth hormone (GH) deficiency [21], in the remaining 70% - 80% provocative tests such as clonidine or glucagon stimulation tests have revealed a peak growth hormone levels lower than those found in patients with constitutional short stature. Potential causative factors for growth failure include iron overload, free radical toxicity, desferrioxamine toxicity [22] zinc deficiency, anaemia, delayed puberty, primary hypothyroidism, liver cirrhosis and defect in the Growth Hormone-Insulin-like Growth Factor-1 (GH-IGF-1) axis. The 62.9% of girls and 69% of boys affected with thalassaemia were less than 2SD below the mean for normal height in a study by Karamifar et al [23]. The prevalence of short stature (<2SD) was 40.6% in a study by Roth et al [24] and 49% as reported by Soliman et al [25]. Moayeri et al [26] showed that 62% of their patients were less than 2SD and 49% were 3SD below the mean values.

Development of secondary sexual characteristics were studied in 11 (4 males and 7 females) adolescent children. Puberty was markedly delayed in all 11 children. Sexual immaturity is a profound complication of severe thalassemia. The incidence rate of failure of onset of puberty is 50% in some studies and may approach even 100% [27]. Multiple gonadal and pituitary-gonadal function studies have confirmed primary gonadal failure due to gonadal iron deposition. Secondary hypogonadism results from iron deposition on gonadotrophic cells of the pituitary gland as shown by poor response of FSH and LH to GnRH stimulation [28,29]. Evidence suggests that, those with more severe defects have a greater rate of iron loading possibly due to increased vulnerability to free radical toxicity. Iron toxicity on adipose tissue has also been shown to cause impaired synthesis of leptin and consequently a delay in sexual maturation [30]. Leptin is a polypeptide hormone produced by adipose cells due to expression of the ob gene and acts as a permissive signal to initiate puberty. Gross iron overload in the pituitary, hypothalamus and gonads is progressive even with chelation therapy [31].

Hypothyroidism was documented in 5 patients in the present study with four children having compensated and one having decompensated hypothyroidism. Thyroid dysfunction is a frequently occurring endocrine complication in thalassaemia major, but its prevalence and severity is variable and the natural history is poorly described. Autoimmunity has no role in the pathogenesis of thalassaemia related hypothyroidism [32]. Up to 5% of thalassaemic patients develop overt clinical hypothyroidism that require treatment whereas a much greater percentage have sub-clinical compensated hypothyroidism with normal T4 and T3 but high TSH levels. It usually occurs in severely anaemic and/or iron overload thalassaemics but is uncommon in optimally treated patients. The pathogenesis is again unclear but thought to relate to lipid perioxdiation, free radical release and oxidative stress. Some studies have reported a high prevalence of primary hypothyroidism reaching up to 17%-18% whereas others have reported a low prevalence of 0% -9% [33]. Shamshirsaz et al [6] demonstrated a prevalence of 7.7% in their study similar to the Italian study group [34] which found 6.2% patients to be hypothyroid where as Aydinok et al [35] showed the higher prevalence at around 16%.

The mean serum calcium was 8.1mg/dl and mean serum phosphate was 5.5gm/dl Hypoparathyroidism was documented in 8 patients. Hypocalcaemia due to hypoparathyroidism is a recognized late and rare complication principally due to iron overload. It has a higher incidence in males and usually evident after 10 years of age . The patients typically have low calcium, PTH & Vitamin D levels and high phosphate levels [27]. The preclinical hypoparathyroidism was recently reported to occur in almost 100% of thalassaemic patients [36] Angelopoulos et al [37] in their study demonstrated hypoparathyroidism in 13.5% subjects with significant low levels of intact parathyroid hormone and total and ionized calcium. Shamshirsaz et al [6] in their multicentre study have shown a prevalence of 7.6%, which was higher than the 3.6% - 7%, reported by other workers and the male: female ratio was 4:1, which was higher than that reported in other studies [34]. Limited data shows that early supplementation with Vitamin D or calcitriol treatment for three months

is sufficient to normalize plasma calcium and phosphate levels [38,39].

Effective management of patients suffering from homozygous beta thalassaemia has led to improved life expectancy and hence manifestations of haemosiderosis related complications, notably, disturbances of the exocrine and endocrine function of the pancreas. But unlike haemochromatosis, where the incidence of diabetes is as high as 80%, the incidence is lower in thalassaemics due to better diagnosis and treatment of the condition [27]. Four out of eight patients of Lassman et al [40] had diabetes where as 50% of twenty patients studied by Suadek et al [41] had abnormal glucose tolerance. Sixteen of eighty two patients interviewed by Chern et al. had diabetes and risk was increased by co-infection with hepatitis C [42]. Gamberini et al [43] followed up 273 thalassaemic patients over a period of thirty years and have shown that 42 patients developed insulin dependent diabetes mellitus. They demonstrated that prevalence progressively increased with time .The Italian working group [34] demonstrated diabetes in 4.9% of patients whereas Aydinok et al [47] showed IGT in 10.8% of their study subjects. A multicentre study showed that 9.4% of thalassaemic patients had diabetes [44]. Although inadequate insulin release has been reported by several groups, hyperinsulinaemia and decreased insulin sensitivity with reduced hepatic release of insulin [6] has been presumed to be the main pathogenic mechanism [45] Glucose intolerance correlates with at least 50% decline in beta cell function which is not entirely reversible even after intensive iron chelation but paradoxically, high transfusion regime not accompanied by effective iron chelation can increase the incidence of diabetes mellitus further [46].

The glucose tolerance test (GTT) was abnormal in 25.5% patients, although none had overt diabetes. The less than expected incidence of diabetes in present study could be explained by the fact that as diabetes is a late complication and majority of patients belong to age group 6-10 years in our group. Serum ferritin level was estimated in 39 patients .

The mean serum ferritin taken after patient had received minimum of 50 units of transfusion ,was not significantly elevated. The reason for this could be fact that serum ferritin gets converted into insoluble hemosidrin when number of transfusion increases as well as the effect of chelation therapy. The mean serum ferritin in children with hypothyroidism was more as compared to thallassemic children with normal thyroid function , however the difference was not statistically significant.similarly no co-relation was found between mean serum ferritin level of thalassemic children with hypothyroidism and those with normal parathyroid status. Also there was no statistically significant relationship of mean serum ferritin levels in children with impaired GTT and children with normal GTT. These findings can be explained by the fact that all the children in our study group were taking chelation therapy regularly which might have modified serum ferritin levels. Also single reading of serum ferritin level taken in these children at one point of time do not truly reflect the chronic damaging effect og iron overload on endocrine glands over the previous years.

Conclusion

Since the quality of life of thalassemia patients is a fundamental aim, it is vital to monitor carefully their growth and pubertal development in order to detect abnormalities and to initiate appropriate and early treatment. Appropriate management shall put in consideration many factors such as age, severity of iron overload, presence of chronic liver disease, thrombophilia status, and the presence of psychological problems. All these issues must be discussed by the pediatrician in charge of the patient's care, the endocrinologist and the patient's family. Regular follow-up is essential for the early detection and appropriate treatment of associated complications. Improvements in protocols of transfusion regime and chelating therapy should improve the care and quality of life of these patients in future. Because any progress in research in the field of early diagnosis and management of growth disorders and endocrine complications in thalassemia should be passed on to and applied adequately to all those suffering from the disease, Recently the role MRI [47] to predict asymptomatic iron deposition in the heart, liver, pancreas, and pituitary gland has received increased attention. Decreased pituitary volume has been observed, which may be due to apoptosis of gonadotropic cells, failure of gonadotropic cells to grow properly, and also the possibility of suppressed leptin level. Patients with transfusion iron overload begin to develop pituitary iron deposition during the first decade of life itself. However significant pituitary volume loss, using mean and standard deviation for a particular age, is not observed until the second to third decade of life. Thus, the critical time for MRI surveillance may be at 10–20 years of age when many patients rapidly accumulate pituitary iron, For children under the age of 7 years, MRI data are lacking. Pituitary volume loss is also an independent predictor of hypogonadism, especially a Z-score of

pituitary volume lower than -2.5 or pituitary height less than 4.4 mm. However, MRI results reveal that many patients with moderate to severe pituitary iron overload retain normal gland volume, representing an opportunity for iron chelation treatment and potential improvement in pituitary function Refrences

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