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Original Research Article

Study of thyroid functions in transfusion dependent thalassemia patients of pediatric age group with reference to serum ferritin level in a tertiary care centre

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ABSTRACT

Introduction: Hypothyroidism is one of the most common endocrine complication in transfusion dependent thalassemia patients. Its prevalence and severity is variable and the natural history is poorly described. The frequency of hypothyroidism in Beta Thalassemia Major (BTM) children ranges from 6 to 30%.

Aim & Objective: To determine the levels of serum TSH and FT4 in patients with transfusion-dependent thalassemia (TDT), as well as their relationship to the degree of iron excess indicated by serum ferritin levels.

Materials and Methods: This observational descriptive study was undertaken on 200 patients (5 to15 yrs of age) in the department of Pediatrics in SCB Medical College, Cuttack, Odisha, India from to after obtaining clearance from institutional ethical committee.

Results: Out of total 200 TDT children, 141(70.50%) were euthyroid and 59(29.50%) were hypothyroid. Among hypothyroid children, 9(4.5%) had overt hypothyroidism and 50(25%) children had subclinical hypothyroidism. In children <10 years of age group there was a positive correlation between serum ferritin and rise in serum TSH ($p < 0.05$, r= .553). The rise in serum ferritin was statistically not significant with fall in serum FT4 ($p < 0.05$, r= .122). In children >10 years of age group, there was positive correlation between serum TSH and serum ferritin ($p < 0.05$,r=.845). There was an inverse relation between rise in serum ferritin and fall in serum FT4 ($p < 0.05$, r= -.406).

Conclusion: Hypothyroidism was associated in significant number of transfusion dependent thalassemia patients. Adequate iron chelation therapy to keep serum ferritin level within normal limit and early detection of hypothyroidism preferably below 10 years of age will prevent hypothyroidism and its complications in transfusion dependent thalassemia.

1. Introduction

About 7% of the world's population is a carrier of a hemoglobin disorder, and that 3,00,000-5,00,000 children are born each year with the severe homozygous state of the disease worldwide.[1,2] Every year approximately 1,00,000 are born with thalassemia in India. The carrier rate for thalassemia gene varies from 1-3% in southern India to 3-15% in Northern India. Earlier most of the thalassemic children died in their early infancy due to improper treatment of the disease and its complications. But now with the availability of better diagnostic and management facilities, this disease has changed its

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course from a disease of high mortality to a disease of high morbidity. Life expectancy for patients with thalassemia major has greatly improved and their hopes are now directed towards attainment of better quality of life. Regular blood transfusion and adequate iron chelation therapy are important factors for treatment and follow up of thalassemia patients.[3] At present, thalassemia major patients after diagnosis are maintained at a pre-transfusion hemoglobin level of 9.5– 10 g/dl.[4] Regular blood transfusion has improved the prognosis of thalassemia, but the accumulation of iron contained in the transfused red cells is responsible for damage to the tissues. In addition to the iron administered with blood, the hyperactive bone marrow favors increased intestinal iron absorption, mediated through the decreased production of hepcidin.[5] The common complications in these patients with transfusion related hemosiderosis are induced heart failure, fatal arrhythmias, osteoporosis, bone pain and bone changes, bile stone formation, increased risk of hepatitis, cirrhosis, delayed puberty, growth retardation, developmental delay, diabetes mellitus, and hypothyroidism.[6] Among these, the endocrine disorders are the most common complications in children with thalassemia major.

Amongst various endocrine complications, thyroid dysfunction is the commonest endocrine dysfunction seen in children with transfusion dependent thalassemia. Its prevalence and severity is variable and the natural history is poorly described.[7,8] The reported thyroid dysfunction seen in patients with thalassemia major includes primary hypothyroidism caused due to iron deposition in thyroid gland, subclinical hypothyroidism, as well as secondary hypothyroidism. The frequency of hypothyroidism shows discrepancy depending on the region, quality of management, and treatment protocols.[9–12] Only a very few paediatric studies on thyroid dysfunction in beta thalassemia are available. In India cost of chelation precludes ideal therapy for majority of the patients and the compliance with transfusion is often not optimal. Therefore there is a possibility that there may be high prevalence of hypothyroidism in such patients and there is high chances of these endocrinopathies beginning at an early age than projected by western studies.[13] This study will provide an overview of thyroid hormone levels in patients with transfusion dependent thalassemia.

2. Aim & Objective

To study thyroid function in transfusion dependent thalassemia patients and its correlation with the degree of iron overload represented by serum ferritin level.

3. Materials and Methods

The study was under taken in the department of Pediatrics SCB Medical College, Cuttack from to after getting clearance from Institutional Ethical Committee. It was an observational study. After getting informed written consent from parents of diagnosed cases of 200 transfusion dependent thalassemia patients were included.

3.1. Inclusion criteria

All cases of transfusion dependent thalassemia aged between 5-14 years admitted to SCBMCH and SVPPGIP, who gave consent.

3.2. Exclusion criteria

1. Patients with congenital thyroid disorders.
2. Patients with sickle cell disease.
3. Critically ill patients.
4. CP child and children with developmental, Delay.
5. Patients with primary pituitary dysfunction.
6. Patients with family history of endocrine dysfunction Patients with CNS malignancy undergone Irradiation.
7. Patients with head trauma.
8. Patients on hormonal therapy.

3.3. Methods

Collection of blood samples: Four ml of venous blood sample were collected from each participant before blood transfusion. Then it was put in a plain container (without anticoagulant) after centrifugation, serum sample was prepared and used for measurement of TSH, FT3, FT4 and Ferritin. Biochemical measurements: The biochemical analyses for serum ferritin, TSH, FT4, FT3 were carried-out using COBAS e 411; a fully auto analyser.

3.4. Serum ferritin

Ferritin is the major soluble iron storage protein from which iron may be mobilized for the synthesis of hemoglobin, myoglobin and other iron containing proteins. It is the body's major iron storage protein. The serum concentration of ferritin gives a quantitative measurement of the amount of storage iron in normal subjects and in those with iron deficiency or overload.

CT scan of brain was done in those patients who were diagnosed as a case of hypothyroidism.

3.5. Statistical analysis

All measured variables for the study groups were presented as mean and standard deviation. Statistical analysis was done using software MS Office and SPSS version 20.0.1. Pearson's linear correlation(r) was used to correlate among serum ferritin, serum TSH,FT4,FT3. The magnitude of

intergroup differences for each of the parameters was quantified by using student's t-test. On the basis of t-values, P values (probability) were calculated to determine the significance of variation between the mean values of individual parameters among the groups of patients studied.

4. Results

Out of total 200 TDT children, 141 were euthyroid (70.50%) and 59 were hypothyroid (29.50%).Table 1 The mean age of euthyroid children and hypothyroid children were 8.98±2.78 years and 12.14±1.48 years respectively. There were 84 boys and 57 girls in euthyroid compared to 40 boys and 19 girls in hypothyroid group. Out of 59 hypothyroid children, 9 (4.5%) had overt hypothyroidism and 50 (25%) children had subclinical hypothyroidism. Table 2

The mean serum ferritin, serum TSH, serum FT3 and serum FT4 of total population were 2353.93 ± 755.01 ng/ml, 4.52 ± 3.41 μIU/L, 5.62 ± 1.31 pmol/L and 14.39 ± 3.62 pmol/L respectively. The mean age, serum ferritin, serum TSH, serum FT3 and serum FT4 of euthyroid children were 8.98 ± 2.78 years, 1962.10 ± 401.27 ng/ml, 2.70 ± 0.89 μIU/mL, 5.76 ±1.00 pmol/L and 15.03 ± 2.86 pmol/L respectively, whereas in hypothyroid children mean age, serum ferritin, serum TSH, serum FT3 and serum FT4 were 12.14 ±1.48 years, 3290.31 ± 465.62 ng/ml, 8.88 ± 3.26 μIU/L, 5.30 ± 1.68 pmol/L and 12.86 ± 4.27 pmol/L respectively.Table 3

In this study, mean age of total study population, euthyroid and hypothyroid were 9.91 ± 2.93 years, 8.98 ± 2.78 years and 12.14 ± 1.48 years respectively. The relation between age with euthyroid and hypothyroidism in total study population was statistically not significant ($p > 0.05$)

The mean ferritin was found to be in total study population, euthyroid and hypothyroid were 2353.925 ± 755.01 ng/ml, 1962.10 ± 401.27 ng/ml and 3290.31 ± 465.62 ng/ml respectively. With increase in serum ferritin level, there was statistically significant increase in prevalence of hypothyroidism ($p < 0.05$).

The mean serum TSH in total study population, euthyroid IU/L and 8.88 ±mIU/L, 2.70 ± 0.89 mand hypothyroid were 4.52 ± 3.41 IU/L respectively. There was positive correlation between serum TSH and hypothyroidism. Rise in serum TSH and prevalence of hypothyroidism was statistically significant ($p<0.05$).

The mean serum FT3 in total population, euthyroid and hypothyroid were 5.62 ± 1.31 pmol/L, 5.76 ± 1.00 pmol/L and 5.30 ± 1.68 pmol/L respectively. Statistical significance could not be determined between serum FT3 and thyroid status in study population.

The mean serum FT4 in total population, euthyroid and hypothyroid were 14.39 ± 3.62 pmol/L, 15.03 ± 2.86 pmol/L and 12.86 ± 4.27 pmol/L respectively. There was statistical significance between serum FT4 and thyroid status in study population.

In 10 years, the mean of serum ferritin, serum TSH, serum IU/L, 5.54mFT3 and serum FT4 were 2704.94 ± 662.43 ng/ml, 5.69 ± 3.89 ± 1.40 pmol/L and 13.77 ± 3.77 pmol/L respectively. Out of 121 children, 9 had subclinical hypothyroidism, 48 had subclinical hypothyroidism and rests were euthyroid.Table 4

In children <10 years, the mean serum TSH was found to be 2.72 ±1.02 □IU/L. There was direct correlation between serum ferritin and serumTSH and rise in serum TSH in relation to rise in serum ferritin was statistically significant ($p<0.05$).Table 5

In children <10 years, the mean serum FT3 was found to be 5.75 ±1.00 pmol/L. Rise in serum ferritin was not statistically significant fall in serum FT3 ($p>0.05$).

In children <10 years, the mean serum FT4 was found to be 15.34 ±2.74 pmol/L. The rise in serum ferritin was statistically not significant with fall in serum FT4 ($p<0.05$)

In children ≥10 years, the mean serum TSH was found to be 5.69 ± IU/L. There was positive correlation between serum TSH and serum ferritin; and rise in serum TSH was statistically significant with rise in serum ferritin ($p<0.05$).

In children ≥10 years, the mean serum FT3 was found to be 5.54 ± 1.40 pmol/L. There was negative correlation between serum ferritin and serum FT3. Fall in serum FT3 in relation to rise in serum ferritin was statistically significant ($p <0.05$).

In children ≥10 years, the mean serum FT4 was found to be 13.77 ± 3.77 pmol/L. There was an inverse relation between serum FT4 with serum ferritin and fall in serum FT4 was statistically significant with rise in serum ferritin level ($p < 0.05$).

Out of total 59 hypothyroid children, 9(4.5%) were overt hypothyroidism (high serum TSH, low serum FT3 and FT4) with 2 girls and 7 boys. And 50(25%) were subclinical hypothyroidism (high serum TSH with normal FT3 and FT4) with 17 girls and 33 boys.

The mean age, serum ferritin, serum TSH, serum FT3 and serum FT4 of overt hypothyroidism were 12.44 ± 4.16 years, 4035.67 ± 1370.34 ng/ml, 15.87 ± 1.65 μIU/L, 2.54 ± 1.65 pmol/L and 4.66 ± 1.68 pmol/L respectively. The mean age, serum ferritin, serum TSH, serum FT3 and serum FT4 of subclinical hypothyroidism were 12.08 ± 1.45 years, 3156.14 ± 300.76 ng/ml, 7.61 ± 1.20μIU/L, 5.80 ± 1.15 pmol/L and 14.33 ± 2.67 pmol/L. Table 6

In this study 61% children showed stunted growth, amongst them 56(45.9%) were hypothyroid.64% children showed underweight, amongst them 56(43.7%) were hypothyroid. There was no correlation found between growth and hypothyroidism. Tables 7 and 8

In children with subclinical hypothyroidism, 42 (84%) were on oral chelation and 8 (16%) were without. Amongst children on oral chelation, 37 (88%) were irregularly taking and 5 (12%) were regularly taking but started late. In children with overt hypothyroidism, 5 (55.6%) were on oral

Table 1: Thyroid status in total study population

Thyroid status	Number of children	Male	Female
Euthyroid	141 (70.5%)	84	57
Hypothyroid	59 (29.5%)	40	19
Total population	200 (100%)	124	76

Table 2: Mean ± standard deviation of different parameters in total study population

Total Population	Age (years)	Ferritin (ng/ml)	TSH (μIU/L)	FT3 (pmol/L)	FT4 (pmol/L)
	9.91 ± 2.93	2353.93 ± 755.01	4.52 ± 3.41	5.62 ± 1.31	14.39 ± 3.62
Euthyroid	8.98 ± 2.78	1962.10 ± 401.27	2.70 ± 0.89	5.76 ± 1.00	15.03 ± 2.86
Hypothyroid	12.14 ± 1.48	3290.31 ± 465.62	8.88 ± 3.26	5.30 ± 1.68	12.86 ± 4.27

Table 3: Analysis of different parameters in relation to thyroid status in total study population

Parameter	Thyroid status	N	Mean	S tandard deviation	p-value
AGE (Years)	Euthyroid	141	8.98	2.78	> 0.05 Not significant
	Hypothyroid	59	12.14	1.48	
FERRITIN (ng/ml)	Euthyroid	141	1962.10	401.27	<0.05 Significant
	Hypothyroid	59	3290.31	465.62	
TSH(μ IU/L)	Euthyroid	141	2.70	1.00	< 0.05 Significant
	Hypothyroid	59	8.88	3.26	
FT3 (pmol/L)	Euthyroid	141	5.76	1.00	0.05 Not significant
	Hypothyroid	59	5.30	1.68	
FT4 (pmol/L)	Euthyroid	141	15.03	2.86	< 0.05 Significant
	Hypothyroid	59	12.86	4.27	

Table 4: Serum ferritin and thyroid indices in study groups

Study group (no of children)	Serum Ferritin (ng/ml)	Serum TSH (μIU/L)	Serum FT3 (pmol/L)	Serum FT4 (pmol/L)
<10 years (79)	1816.29 ± 481.63	2.72 ± 1.02	5.75 ± 1.00	15.34 ± 2.74
>10 years (121)	2704.94 ± 662.43	5.69 ± 3.89	5.54 ± 1.40	13.77 ± 3.77

Table 5: Analysis of different parameters in relation to serum ferritin levels in different age group

Age (years)	N	Parameters	Mean	Standard deviation	p-value	Pearson Correlation (r)
<10	79	Ferritin (ng/ml)	1816.29	481.63	< 0.05 Significant	0.553
		TSH (μU/L)	2.72	1.02		
<10	79	Ferritin (ng/ml)	1816.29	481.63	>0.05 Not significant	0.075
		FT3 (pmol/L)	5.75	1.00		
<10	79	Ferritin (ng/ml)	1816.29	481.63	> 0.05 Not significant	0.122
		FT4 (pmol/L)	15.34	2.74		
≥10	121	Ferritin (ng/ml)	2704.94	662.43	< 0.05 Significant	0.845
		TSH (μU/L)	5.69	3.89		
≥10	121	Ferritin (ng/ml)	2704.94	662.43	< 0.05 Significant	0.339
		FT3 (pmol/L)	5.54	1.40		
≥10	121	Ferritin (ng/ml)	2704.94	662.43	< 0.05 Significant	0.406
		FT4 (pmol/L)	13.77	3.77		

Table 6: Type of hypothyroidism with different parameters in study population

Type (no of children)	Age (years)	Serum Ferritin (ng/ml)	Serum TSH (μIU/L)	Serum FT3 (pmol/L)	Serum FT4 (pmol/L)
Overt (9)	12.44 ± 4.16	4035.67 ± 1370.34	15.87 ± 1.65	2.54 ± 1.65	4.66 ± 1.68
Subclinical (50)	12.08 ± 1.45	3156.14 ± 300.76	7.61 ± 1.20	5.80 ± 1.15	14.33 ± 2.67

Table 7: Height distribution in study population

Percentiles	No of children	Percentage (%)	Hypothyroidism
<3rd	122	61	56
3 rd -10th	36	18	2
10th -50th	33	16.5	1
50th -90th	9	0.045	0
90th -97th	0	0	0
>97th	0	0	0
Total	200	100	59

Table 8: Weight distribution in study population

Percentiles	No of children	Percentage (%)	Hypothyroidism
<3rd	128	64	56
3 rd -10th	29	14.5	2
10th -50th	37	18.5	1
50th -90th	6	0.03	0
90th -97th	0	0	0
>97th	0	0	0
Total	200	100	59

chelation and 4 (44.4%) were without. Amongst children on oral chelation, all were irregularly taking. CT scan of brain was done in children with hypothyroisism was found to be normal.

In this study, mean age at which transfusion was started in hypothyroidism was 7.54 ± 2.51 months and in euthyroid was 6.49 ± 2.35 months. Early age at which transfusion started was statistically significant with hypothyroidism ($p < 0.05$). Table 9

5. Discussion

The thyroid gland has a critical role in the maintenance of thermogenic and metabolic homeostasis.[13] It secretes two important hormones namely thyroxine (T4) and triiodothyronine (T3). These hormones play a very important role in controlling metabolic activity and affect the function of allorgans.[14] After approximately one year of transfusion, iron starts to accumulate in parenchymal tissues, where it leads to substantial toxicity as compared with iron stored in reticulo-endothelial cells.[15] Thalassemia is one of the most important genetic diseases and thyroid dysfunction which is well documented in these patients. Iron overload of tissue is the most important complication of beta-thalassemia and is a major subject of management.[16] TDT children on regular transfusions and suboptimal chelation are at an increased risk for iron overload. Like in all organs, iron is deposited in the thyroid interstitium resulting in thyroid hemosiderosis.

A wide spectrum of pathogenic mechanisms is involved. Chronic tissue hypoxia and iron overload have a direct toxic effect on the thyroid gland.[17] High concentrations of labile plasma iron and labile cell iron which are considered to be responsible in the formation of free radicals and the production of reactive oxygen species may lead to cell and organ damage.[18] This study aimed at evaluating thyroid dysfunction in transfusion dependent thalassemia in paediatric age group and its correlation with serum ferritin level was analysed. A total 200 children of TDT were enrolled in this study. Out of which 124 were male and 76 were female. Mean age of the total study population was 9.91 ± 2.93 years.

The prevalence of hypothyroidism in thalassemia major patients ranges from 3.3% to 37.5%% in various different studies worldwide. Age group, treatment methods and iron chelation therapy are involved in prevalence of hypothyroidism in different centers.[19] In 1983, A R Sabato et al found the presence of primary hypothyroidism (uncompensated and compensated) was associated with an age of at least 10 years, an increased incidence of iron toxicity-related systemic complications, and an increased transfusion iron load, but not with an increased serum ferritin level.[20] In 1995, a multicentre study conducted in Italy and they found primary hypothyroidism in 6.2% (mean age 15.8 years) out of 1861 patients of beta thalassemia.[21] In 1997, C E Jansen et al found a positive correlation was demonstrated between serum ferritin concentrations and the presence of thyroid dysfunction.[22] In 2002, a study done by Aydinok et al found mean ferritin concentrations was 3597 ± 1931 ng/ml.Growth retardation was found in 40 per cent of patients.

Hypothyroidism was observed in 16 per cent of patients.[23] In 2003, Alireza A Shamsirsaz et al in Tehran found primary hypothyroidism was present in 7.7% of the patients of beta thalassemia.[24]

In 2004, A Zervas et al found normal thyroid hormone values in 167 (83.5%) of the 200 patients studied. Eight (4%) of the remaining patients had overt hypothyroidism,

Table 9: Analysis between age at which transfusion started and thyroid status

Parameter	Thyroid status	N	Mean	Standard deviation
Age at which transfusion started (months)	Euthyroid	141	7.54	2.51
	Hypothyroid	59	6.49	2.35
P < 0.05 (Significant)				

and 25 (12.5%) had subclinical hypothyroidism. Mean ferritin levels in hypothyroid and euthyroid patients were 2707.66 ± 1990.5 ng/ml and 2902.9 ± 1997.3 ng/ml respectively, (p = 0.61), indicating no correlation between ferritin levels and thyroid functional status.[25] In 2006, in a study done by Filosa A et al on 50 patients of beta thalassemia major over a period of 12 years found five (28%) out of 17 patients had subclinical hypothyroidism. Four out of twelve patients with previous subclinical hypothyroidism showed worsening with a different degree of severity: two females changed to compensated hypothyroidism, and two males to overt hypothyroidism.[26] In 2007, a multicentre study in Cyprus by Meropi Taumba et al including 435 patients showed hypogonadotrophic hypogonadism in 32.5%, short stature in 35%, acquired hypothyroidism in 5.9%, hypoparathyroidism in 1.2% and diabetes mellitus in 9.4%.[27] In 2008, a study in Iran by Farzad Najafipour et al observed primary overt hypothyroidism in 16% of patients.[28] In 2008, a study conducted by MR Gamberini et al on 273 patients with thalassemia major followed from diagnosis in the Ferrara Centre found primary (80%) and central 20%) hypothyroidism in 31% of patients.[29] In 2008, WA Mula-Abed et al conducted cross-sectional study on 30 Omani patients with transfusion dependent homozygous beta-thalassemia major and found primary hypothyroidism was present in only 1 (3.3%) patient (female). There was no significant difference (p > 0.050) in mean serum ferritin in thalassemics with or without endocrinopathy, regardless of the number of endocrinopathy.[30] In 2011, Pieman Eshraghi et al found short stature in 41(31.3%) patients. In 53(40.8%) patients, weight was under normal range. Hypothyroid was found in 19 patients (14.6%); 2 primary overt hypothyroidism, 3 secondary hypothyroidism and 14 subclinical hypothyroidism were detected. Correlation between HT and serum ferritin level was not significant (p=0.584) but it was significant for HT and short statures (p=0.002), also regular transfusion and chelation therapy were correlated with ferritin level.[31] In 2012, Fatemeh Safari et al conducted a cross- sectional study on 77 patients with β thalassemia major (15-36 years old) and found hypothyroidism in 18.2% of patients.[32] In 2013, in a study done by Soliman Ashraf T et al on a total of 48 patients (22 males and 26 females) over a 12 year-period of follow-up found hypothyroidism was diagnosed in 17/48 (35%) of patients. There was no significant difference in the prevalence in males 7/22 (32%) versus females 10/26 (38%). Sixteen of the patients had hypothyroidism after the age of 10 years (94%), three patients (6.3%) had subclinical hypothyroidism. There was a significant negative correlation between serum ferritin and FT4 (r = - 0.39, P = 0.007), but no correlation was found between ferritin and TSH.[33] In 2013, Valeria Chirico et al found patients with thyroid dysfunction were characterised by higher ferritin when compared with patients without thyreopathies. Patients with ferritin values above 1800g/l experienced a significantly faster evolution to endpoint. Ferritin predicted high risk of thyroid dysfunction independently of confounding factors.[34] In 2013, Taysir S et al found the prevalence of subclinical hypothyroidism in patients with β-TM was 15.4%, with significantly higher mean serum TSH compared with controls and positively correlated with the serum ferritin level.[35] In 2016, Rajni Sharma et al studied on 89 patients of thalassemia major and found primary hypothyroidism (subclinical) present in 8·9% of patients.[36] In 2016, Kanwal Jehanzeb et al found out of 56 patients, 21 (37.5%) had biochemical evidence of hypothyroidism. Mean Ferritin level was 3924 ± 1247ng/ml in hypothyroid and 3136 ± 1387ng/ml in euthyroid patients indicating a significant difference in mean serum ferritin levels between hypothyroid patients and others.[37] In 2017, in Iran Farideh Mogharab et al studied on 112 patients, thyroid hormone level was normal in 106 of 112 total examined patients (94.6%). Six patients (5.4%) suffered from hypothyroidism. Mean ferritin levels in patients with hypothyroidism and euthyroid were respectively as 3200-5000 mg/l and 2413-2830 ng/ml. Therefore, there was a direct relationship between prevalence of hypothyroidism and serum ferritin level.[38]

In 2018, in southeast of Iran Ali Bazi et al studied on a total of 103 (53.1%) and 91 (46.9%) females and males respectively. The mean age of the patients was 15 ± 7.5 years. HT showed overall frequencies of 8.2% (18/194). Subclinical and overt HT were observed in 13 (6.7%) and 5 (2.6%) patients, respectively. There was no significant association between HT and age. The ferritin level was correlated with HT.[39] In 2018, a study done by SH Upadya et al at KMC Hospital mangalore on study population of 83 children consisted of 49 boys (59%) and 34 girls (41%). 4.8% of the children had evidence of subclinical hypothyroidism.

Among them two belonged to the first decade and the other two to the second decade of life. Mean TSH, FT4, and ferritin values among children with thyroid dysfunction were 6.38 ± 0.83mIU/L, 1.08 ± 0.45ng/ml and3983.0 ±1698.30ng/ml respectively.[40] In 2019, in Turkey HH sahin

and I dogan found the prevalence of hypothyroidism was 22.6%, and the prevalence of primary hypothyroidism was 14.6%. Mean ferritin levels were determined as 5283.64 ± 2023.95 ug/L and 1868.67 ± 955.98 ug/L respectively for patients with hypothyroidism, and euthyroidism; and a significant difference was determined between the two groups (p=0.001). Thyroid dysfunction was encountered more frequently in patients receiving four units of blood transfusion per month, and high dose chelation therapy (both p=0.001). Severity of thyroid dysfunction was determined to have a statistically significant relationship with increased serum TSH, and decreased serum FT4 levels.[41]

In 2020, Singhal A et al studied on a total of 112 children, 82 were Euthyroid (73.2%) and 30 were Hypothyroid (26.8%). The mean serum ferritin, serum TSH, serum free T4 and serum free T3 in euthyroid children were 1975.4 ± 706.2(ng/ml), 3.23 ± 0.93(μIU/ml), 12.8 ± 2.3(pmol/l) and 6.12 ± 1.4(pmol/l) respectively. Whereas in Hypothyroid children the mean serum Ferritin, serum TSH, serum Free T4 and serum Free T3 were 2842.9 ± 1095.2(ng/ml), 7.05 ± 1.91(μIU/ml), 10.55 ± 2.0(pmol/l) and 4.49 ± 1.2(pmol/l) respectively. The incidence of hypothyroidism directly related to degree of iron overload measured by serum ferritin level.[42] The findings of this study revealed that out of 200 patients of transfusion dependent thalassemia, 59(29.5%) children had thyroid dysfunction in form of hypothyroidism. Rest 141(70.5%) had thyroid status within normal range. The prevalence of hypothyroidism in our study was in accordance with studies done by Filosa A et al,[26] MR Gamberini et al[29], Khider and Hussein,[43] and Singhal A et al,[42] while other studies showed a lower prevalence rate of hypothyroidism in beta thalassemia major patients.

The mean serums TSH, serum FT3, serum FT4 of hypothyroid children in study population were 8.88 ± 3.26 μIU/L, 5.30 ± 1.68 pmol/L and 12.86 ± 4.27 pmol/L respectively. Subclinical hypothyroidism was the most common thyroid abnormality observed in study population with total no of 50(25%) children, it was supported by Filosa A et al,[26] R Sharma et al[36] and Abdel Razek et al[44], where subclinical hypothyroidism was most frequently reported. Out of 50 subclinical HT children 17(8.5%) were female and 33(16.5%) were male.

Overt hypothyroidism observed in total 9(4.5%) children. Out of 9 overt HT children, 2(1%) were female and 7(3.5%) were male. No correlation observed between thyroid status and gender of the population which was supported by Farideh Mogharab et al.[38] No correlation was noticed between euthyroid and hypothyroid with age in total study population(p>0.05). However more number of hypothyroid children were > 10 years age group, similar to studies done by Garadah et al,[45] WA Mula-Abed et al,[30] Filosa A et al,[26] A Zervas et al,[25] where thyroid dysfunction was seen in the second decade of life.

All children with hypothyroidism had high serum ferritin level despite chelation with mean ferritin level of 3290.31 ± 465.62 ng/ml, similar to study done by Singhal A et al,[42] A Zervas et al[25] and Ayfer Gozu Pirincciogluu,[46] where the mean ferritin values among the hypothyroid group were 2842.9 ± 1095.2 ng/ml, 2707.66 ± 1990.5 ng/ml and 2703 ± 1649 ng/ml, respectively.

In this study there was statistical significance between serum TSH with serum ferritin level in both <10 years and >10 years (p<0.05). However significance with serum FT3 was only found in age group >10yrs. It was supported by C E Jansen et al,[23] Farideh Mogharab et al[38], Valeria Chirico et al,[34] Taysir S et al,[35] Kanwal Jehanzeb et al,[37] and Singhal A et al,[42] which proved ferritin as a prognostic marker for TDT patients and showed direct relationship between prevalence of hypothyroidism and serum ferritin level in contrast with study done by A Zervas et al,[25] WA Mula Abed et al,[30] as they observed no correlation between thyroid status and serum ferritin. However study done by Soliman Ashraf T et al[33] found a significant negative correlation between serum ferritin and FT4 but no correlation was found between ferritin and TSH. Mean age at which transfusion was started in hypothyroid and euthyroid children were 7.54 ± 2.51 months and 6.49 ± 2.35months respectively. Early age at which transfusion started was statistically significant with prevalence of hypothyroidism (p<0.05), similar to study done by Singhal A et al.[42] On anthropometric assessment which was conducted for all children included in this study and found that 64% were wasted and 61% stunted for age. In contrast to Pieman Eshraghi et al,[31] where 31% patients were short stature and 40% were wasted.

6. Limitation of the Study

In view of financial reasons we were not able to look into the cause of hypothyroidism, wheather primary or secondary, hence this needs further study.

7. Conclusion

This study demonstrated hypothyroidism in significant number of transfusion dependent thalassemia patients. Subclinical hypothyroidism was the most common finding. There was significant association present between serum ferritin and the presence of thyroid dysfunction, emphasizing the important role of iron overload in the development of hypothyroidism. Hypothyroidism was observed mostly in those on irregular iron chelation or without chelation and there was increase in prevalence of hypothyroidism in those who had started transfusion early compared to those who had started late. It suggests iron overload has direct role in causation of hypothyroidism. It signifies the importance of monitoring thyroid function in all TDT patients as well as need of chelation in time.

Patients, who have subclinical hypothyroidism, should be followed up annually and to treat those, who have overt hypothyroidism. Pharmacological treatment for hypothyroidism is readily available, it is important to monitor thyroid function and institute prompt therapy when indicated. Iron overload induced hypothyroidism may respond to adequate chelation therapy promoting prevention or/and reversal of the disease and other associated co morbidities. Treatment of overt hypothyroidism should be done with l-thyroxin along with treatment of iron overload with chelators. The prevalence and severity of thyroid dysfunction in thalassemics is variable, and regular follow-up is the key. Assessment of thyroid function should be done annually from the age of 9 years or earlier if patient is clinically symptomatic. In this study, prevalence of hypothyroidism indirectly suggests degree of iron overload in the study population. So a regular follow up and an early intervention should be taken in the form of regular chelation to avoid morbidities associated with iron overload.

8. Authors Contribution

1. Tanuja Mohapatra - Literature, Data collection.
2. Swarupa Panda - Study concept, Research design.
3. Bipsa Singh - Data compilation, Method.
4. Bibhu Prasad Nayak - Data analysis, Manuscript preparation & Editing.
5. Mangal Charan Murmu - Method, Manuscript preparation & Editing, Coordination.

9. Source of Funding

None.

10. Conflict of Interest

None.

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