Endocrinopathies and its relationship with Thalassemia

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ABSTRACT
Thalassemia is a common genetic blood disorder that places a burden on patients and the healthcare system, particularly in developing countries. Thalassemia is an inherited hemoglobinopathy that is transmitted to an individual as a result of a gene mutation that creates the alpha or beta-globin chains. Unless the genes are defective for beta chains, it may result in beta-thalassemia. If both beta genes are defective, the person has significant thalassemia and extreme anemia. Thalassemia is associated with several disorders of the endocrine that include pituitary, thyroid, pancreas, gonads, parathyroid and bone. This cross-sectional study was carried out on 100 Thalassemia patients, and 100 healthy controls and the levels of Minerals, Hormones, Diabetic Profile and Vitamin D was assessed in both the groups. Vitamin D deficiency was the commonest endocrine complications, followed by LH/FSH deficiency, hypothyroidism (32%), diabetes mellitus (6.7%) hyperparathyroidism and adrenal insufficiency. There was more number of male then female patients with hypogonadism. Seven out of thirty-two patients with hypothyroidism presented with subclinical hypothyroidism. In our study total, 41% of patients had Vitamin D deficiency, 13 % had vitamin D insufficiency, and 46% had sufficient levels. Diabetes Mellitus with high fasting levels was seen in 16% of patients. In our study, 10% of patients had no Endocrine Disorder. The present study suggests that early screening programs for iron overload should be implemented to prevent endocrinopathies in children and adults and supplemented with prophylactic vitamin D.

INTRODUCTION
Thalassemia is a common genetic blood disorder that places a burden on patients and the healthcare system, particularly in developing countries. (Weiss et al., 2019) Thalassemia is an inherited hemoglobinopathy that is transmitted to an individual as a result of a gene mutation that creates the alpha or beta-globin chains. Unless the genes are defective for beta chains, it may result in beta-thalassemia. If both beta genes are defective, the
A number of these complications arise from the iron overload caused by frequent transfusions. (Shamshirsaz et al., 2003) Excessive iron is concentrated in most of the body’s tissues, including the liver, heart, and endocrine glands. (Al-Elyq and Hh, 2004) Iron accumulation in tissues leads to endocrine dysfunction, a well-recognized complication in patients with transfusion-dependent thalassemia. (Flynn et al., 1976; Masala et al., 1984) The impact of iron toxicity on endocrine glands has been well illustrated in numerous histological studies. (Abdulzahra et al., 2011; Mahmoodi et al., 2011) Endocrine complications in patients with thalassemia: delayed puberty, diabetes mellitus, hypothyroidism, and hypoadrenalism are some of the complications in thalassemia patients. (Tiosano and Hochberg, 2000; Gulati et al., 2000) The most significant cause of hypogonadism is gonadal iron accumulation resulting in primary gonadal failure. (Kuo et al., 1968) Chronic blood transfusion (CBT) is the cornerstone of treatment for people with β-thalassemia major (BTM) to avoid growth retardation, skeletal changes resulting from bone marrow expansion, and mass development from extramedullary hematopoiesis.

Despite this, CBT causes iron-overload, which requires long-term iron chelation therapy to control and manage. The primary causes of death are insufficient chelation therapy, cardiac arrhythmias, cardiomyopathy, and heart failure, while endocrine defects and chronic liver disease contribute greatly to morbidity and mortality. The iron chelation therapy will usually be begun as soon as the patient is filled with iron. A significant iron load amounts to about 1,000 ng / mL of serum ferritin. The concentration of liver iron (LIC) is considered the best indicator of the total iron charge. Before beginning chelation, LIC should have a dry weight of at least 3 mg Fe /gram (Galanello and Origa, 2010). Thyroid dysfunction in patients with thalassemia has been reported with varying degrees of prevalence.

For example, Najafipour and colleagues showed a 16 per cent prevalence of thalassemia hypothyroidism in their patients, while other authors reported a 13-60 per cent prevalence of hypothyroidism. The authors hypothesized that its patients will be affected by more subclinical forms of hypothyroidism (Najafipour et al., 2008). It should be noted that thyroid dysfunction and the use of levothyroxine will increase the risk of bone mineral depletion (Espallargues et al., 2001; Mohammadi et al., 2007). Hb E/β-thalassemia accounts for over 50 per cent of the burden of thalassemia disease in the Indian state of West Bengal (Mandal et al., 2014).

**Aim**

To study endocrinopathies and its relationship with
thalassemia.

Objective
To correlate the levels of minerals, Hormones, Diabetic Profile and Vitamin D levels between patients and healthy controls (age-matched) attending AVBRH Wardha and SMHRC Nagpur.

MATERIALS AND METHODS
The present study was carried out in the Department of Biochemistry and General Medicine at Datta Meghe Medical College, Shalinitai Meghe Hospital and Research Centre, Nagpur in collaboration with Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Sawangi (Meghe) Wardha Maharashtra.

Total of 200 subjects were selected for the study. Out of which 100 patients are age and gender-matched healthy control, 100 were suffered from Thalassemia. Informed consent was taken from all participants included in the study.

Sample Collection
Blood sample were collected, and all patients and controls (n=200) gave informed consent for participation to the study. Vitamin D was estimated by Dry Chemistry analyzer. Electrolyte levels were measured by electrolyte analyzer, as electrolyte analyzer has different electrodes, specific for different ions of interest. Each electrode has an ion-selective membrane that undergoes a specific reaction with the corresponding ions contained in the sample being analyzed. Levels of Hormones, Alkaline phosphatase and ferritin was measured by Dry Chemistry analyzer.

Inclusion Criteria
All patients with thalassemia are selected for the study.

Statistical Analysis
All estimated results were expressed as mean ±SD. Mean values will be assessed for significance by unpaired student -t-test. Statistical analysis will be performed using the Statistical Package for the Social Science program (SPSS, 24.0). Frequencies and percentages will be used for the categorical measures. Probability values p < 0.05 will be considered statistically significant.

RESULTS AND DISCUSSION
Thalassemia derives from the Greek words Thalassa meaning "water" and haema means "of blood." It was first identified in people living in the Mediterranean, the Middle East and South-East Asia. Thalassemia can now be found across the globe, however, due to widespread migration. Every year on May 8, World Thalassemia Day is celebrated to raise awareness of the disease among the public. The clinical continuum of thalassemia involves asymptomatic carriers to the main patients with serious thalassemia who require lifelong blood transfusions and iron chelation. Optimal iron overload regulation increases survival, but this improved lifespan is associated with a higher complication burden. Endocrine defects are among major β-thalassemia complications.

The iron which is metabolically active is stored in endocrine organs. Timely chelation of the iron can reduce hyperferritinemia, thereby improving endocrinopathies. Thalassemia is associated with several disorders of the endocrine that include pituitary, thyroid, pancreas, gonads, parathyroid and bone. Bone disease Thalassemia is a widespread but poorly understood condition that affects both younger and relatively older cohorts of patients. The multiple factors which contribute to bone loss pose a diagnostic and therapeutic challenge. The May 2019 issue of the Indian Journal of Child Health publishes an article by Katakai and Bharati, where authors identified the effect of ferritin levels in early detection of endocrinopathy among 70 children aged 5–18 from northeastern India (Katakai and Bharati, 2019).

In understanding endocrine problems, current literature stressed the use of judicious blood transfusions and serial ferritin measurement (Sanctis, 2002). Hypophyseal damage from iron overload is the underlying pathogenetic cause in hypogonadism and leads partly to poor growth (Kyriakou and Skoridis, 2009). Puberty is the stage of an insult to full development. The standard protocol is to initiate iron chelation therapy when the amount of serum ferritin exceeds 1000 ng/ml or when the child exceeds 3 years of age or has obtained approximately 10–20 transfusions. In this study, we saw the role of endocrinopathies in patients attending AVBRH Wardha with thalassemia showed in Table 2.

In our study, we have taken 100 patients out of which 52 were male, and 48 were female showed in Table 4. In all 90.0% of all patients suffered from at least one endocrine complication, 70% have one endocrinopathy, 48.9% with two types of endocrinopathies and 15.1% of them have three or more types of endocrinopathies. Vitamin D deficiency was the commonest endocrine complications, followed by LH/FSH deficiency, hypothyroidism (32%), diabetes mellitus (6.7%) hyperparathyroidism and adrenal insufficiency showed in
Table 1: Clinical characteristics of Patients

| Endocrinopathy                  | No. of Patients | Female | Male | Mean Age |
|--------------------------------|----------------|--------|------|----------|
| Diabetes Mellitus              | 16             | 7      | 9    | 12       |
| Hypothyroidism                 | 32             | 18     | 14   | 11.30    |
| LH/FSH Deficiency              | 35             | 16     | 19   | 15.4     |
| Short Stature                  | 22             | 7      | 15   | 12.81    |
| Hyperparathyroidism            | 12             | 8      | 4    | 12.47    |
| Adrenal Insufficiency          | 8              | 3      | 5    | 13       |
| Vitamin D Deficiency           | 54             | 28     | 26   | 10.54    |

Table 2: Concentration of Biochemical Parameters in thalassaemic patients

| Biochemical Parameters | Thalassemia patients | Healthy controls | T-test | P-value |
|------------------------|----------------------|------------------|--------|---------|
| Hb                     | 7.8±2.379            | 13.3±4.392       | 11.011 | <0.0001 |
| Serum Ferritin         | 645.56±363.97        | 178.35±337.98    | -9.406 | <0.0001 |
| Fasting Blood Sugar    | 154.8±24.92          | 80.48±12.34      | -26.726| <0.0001 |
| Glycated Hb            | 7.9±1.9              | 5.4±0.9          | -11.891| <0.0001 |
| Sodium                 | 147.21±7.08          | 1384.5±9.8       | -7.246 | <0.0001 |
| Potassium              | 7.4±5.26             | 4.5±3.21         | -4.706 | <0.0001 |
| PTH                    | 108.65±19.82         | 14.39±2.3        | -47.241| <0.0001 |
| Morning Cortisol       | 6.2±1.83             | 17.31±3.41       | 28.708 | <0.0001 |
| T3                     | 109.45±22.064        | 164.18±31.31     | 19.026 | <0.0001 |
| T4                     | 3.14±1.024           | 9.31±1.41        | 35.407 | <0.0001 |
| TSH                    | 8.15±1.95            | 2.5±0.89         | -26.359| <0.0001 |

Table 3: Result of Vitamin D, Calcium, Alkaline phosphatase and phosphorous

| Variables               | Patients       | Control       | t value | P-value |
|-------------------------|----------------|---------------|---------|---------|
| Serum Vitamin D         | 19±6.31        | 38.65±4.02    | 11.746  | <0.0001 |
| Deficiency              | 41             |               |         |         |
| Insufficiency           | 13             |               |         |         |
| Sufficiency             | 46             |               |         |         |
| Alkaline Phosphatase    | 421.34±189.34  | 126±52.84     | -6.719  | <0.0001 |
| Serum Calcium           | 8.42±0.71      | 9.76±0.42     | 7.265   | <0.0001 |
| Serum Phosphorous       | 2.82±0.43      | 3.20±0.44     | 2.762   | 0.0088  |

Table 4: Levels of Gonadal and Pituitary Hormones in Patients and Healthy Controls

| Variables   | Patients       | Control       | t-value | P-Value |
|-------------|----------------|---------------|---------|---------|
| LH          | 0.82±0.40      | 3.02±0.98     | 12.240  | <0.0001 |
| FSH         | 1.21±0.70      | 2.84±1.98     | 4.592   | <0.0001 |
| Prolactin   | 19.93±2.78     | 14.85±5.60    | -4.239  | 0.001   |
| Estrogen    | 20.42±5.89     | 34.53±8.02    | 8.389   | <0.0001 |
| Testosterone| Male N=52      | 34.61±24.920  | 351.72±427.77 | 5.337  | <0.0001 |
|             | Female N=48    | 2.18±0.86     | 23.69±19.44 | 7.656  | <0.0001 |
Table 1 and Table 4. There was more number of male then female patients with hypogonadism. Seven out of thirty-two patients with hypothyroidism presented with subclinical hypothyroidism. In our study total, 41% of patients had Vitamin D deficiency, 13 % had vitamin D insufficiency, and 46% had sufficient levels showed in Table 3. Diabetes Mellitus with high fasting levels was seen in 16% of patients. In our study, 10% of patients had no Endocrine Disorder.

CONCLUSIONS

Thalassemia is an inherited blood disorder; prompt identification of these disorders by screening should be done in all patients to facilitate care as soon as possible, education programs should be placed in a place for the production and tracking of early detection and replacement therapy in which endocrine abnormalities may be minimized in future. Deficiency of vitamin D, delayed puberty, short stature, hypothyroidism are common complications of iron overload. The present study suggests that early screening programs for iron overload should be implemented to prevent endocrinopathies in children and adults and supplemented with prophylactic vitamin D.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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