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Study of Association of Anemia in Sub-clinical and Overt Hypothyroid Patients.

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ABSTRACT

Anemia is one of the commonest nutritional disorders affecting Indian population and hypothyroidism adds to the burden of anemia in them. Subclinical and Overt Hypothyroidism affects about 4 - 8.5% and 2 - 5% respectively of the adult population world over. Thyroid hormones stimulate directly or indirectly growth of erythroid colonies through erythropoietin. Hypothyroidism can cause a wide variety of hematological disorders and anemia could be its first manifestation. Numerous mechanisms are involved in the pathogenesis of these anemias that can be microcytic, macrocytic and normocytic. The aim of the present study was to estimate the frequency and type of anemia in sub- clinical and overt hypothyroidism patients. The present case control study included 231 patients of which 123 were subclinical hypothyroid cases, 108 were overt hypothyroid cases and 209 age and sex matched healthy controls. Hb levels were measured in both case and controls. Peripheral smears of the anemic patients were examined. Serum iron, ferritin, vitamin B12 and folic acid were measured in both subclinical and overt hypothyroid patients. Anemia prevalence was 49.3% in the overt hypothyroid group, 46.8% in the subclinical hypothyroid group, and 28% in the control group. Thus, the frequency of anemia in subclinical hypothyroidism is as high as that in overt hypothyroidism. Hb levels were significantly lower in overt cases than in Sub-clinical hypothyroid cases. Anemia of chronic disease was the commonest type in both sub-clinical and overt hypothyroidism cases. Vitamin B12, Fe, and folic acid levels were similar between these groups. According to our study, anemia of chronic disease is the most common type of anemia in hypothyroid patients. Suspicion of Hypothyroidism should be considered in anemias with uncertain etiology.

Keywords: *anemias, subclinical hypothyroidism, overt hypothyroidism, anemia of chronic disease.*

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INTRODUCTION

Anemia is one of the common disorders affecting Indian population which may be further influenced by Hypothyroidism. The prevalence of hypothyroidism differs from country to country and ranges from 2-5% of the population all over the world. The prevalence of sub-clinical hypothyroidism is even more at a range of 4-8.5%, which may increase up to 20% after 60 years of age [1]. In India due to ignorance and carelessness, many overt hypothyroid and sub-clinical hypothyroid patients remain undiagnosed. In India a recent study reported prevalence of hypothyroidism as 3.9% and sub-clinical hypothyroidism as 9.4% in adults [2].

Hypothyroidism leads to deceleration of metabolic activity in the body. Almost all organ systems are affected and the severity of signs and symptoms depends on the age of occurrence and deficiency status of hormones. Hematopoietic system is one of the primary systems affected by hypothyroidism and anemia is the most common manifestation. Hypothyroidism can cause a wide variety of anemic disorders. Numerous mechanisms are involved in the pathogenesis of these anemias that can be microcytic, macrocytic and normocytic. The most frequently encountered anemia type is normochromic normocytic anemia. The most frequent reason of this is the bone marrow repression due to thyroid hormone deficiency which also causes defective erythropoietin production . Erythrocyte life cycle in hypothyroidism is normal, and there is hypo proliferative erythropoiesis. Thyroid hormones also increase 2-3 DPG (di-phosphoglycerate) levels assisting in the transmission of oxygen into the tissues [3,5].

Pernicious anemia can accompany hypothyroidism as a constituent of Polyglandular autoimmune syndrome. Failure of vitaminB12 absorption occurs in pernicious anemia due to Intrinsic Factor (IF) deficiency and gastric achlorhydria.This is the reason of macrocytic anemia occurrence in hypothyroidism [6]. Folic acid is another vitamin with impaired intestinal absorption, may cause macrocytic anemia in hypothyroidism [7].

Iron deficiency anemia is related with menorrhagia occurring as a result of various hormonal imbalances and also malabsorption which is seen in hypothyroidism [8,9].

Therefore the aim of our present study was to establish association of anemia in terms of frequency and types in subclinical and overt hypothyroid patients.

MATERIALS AND METHODS

The present study was conducted at Sri Siddhartha Medical College Hospital and Research centre Tumkur from October 2013 to September 2014.

The patient's group consisted of 231 recently diagnosed, non-treated Hypothyroid cases (overt=108, subclinical=123) with mean age 48.41±11.65 yrs. The study also included 209 healthy age and sex matched controls that had normal thyroid hormone levels.

The cases were selected randomly each day from subjects attending the out-patient's Clinics of Medical and General Surgery departments of Sri Siddhartha Medical College Hospital (SSMCH) and from subjects referred to the Central Laboratory from other specialties for investigations. The control group was selected from persons attending outpatient clinics of various departments whose history, clinical examination and investigations did not reveal any major illness including that of thyroid status.

This study was approved by The Institutional Research Ethics Committee and informed consent was obtained from each participant.

The exclusion criteria were

- Multifactorial anemia or anemia due to other reasons including hemolytic anemias, gastrointestinal or genitourinary losses due to malignancy and/or acute/sub acute blood losses from the respiratory, gastrointestinal, or genitourinary tract.

- Prior thyroid disorder and/or treatment history, presence of any co-morbid disease like renal insufficiency/failure, coronary heart disease, uncontrolled hypertension, diabetes mellitus, or any endocrine system disease other than hypothyroidism.

- Patients who were under the treatment that might affect blood parameters such as steroids or who had received anemia treatment previously were excluded from the study.

With aseptic precautions, 7 ml of venous blood was drawn from both cases and controls in the fasting state. The separated serum and whole blood were analyzed. Serum Free T3, Free T4 and TSH were measured by Electrochemiluminescence Immuno Assay method. Serum Iron, Iron binding capacity, Ferritin, Vitamin B12 and Folic acid levels were measured by Immuno assay method using Cobas Analyzer. EDTA samples were used for Complete blood count using Sysmex Fully Automated Hematology Analyzer. Peripheral smears of anemic patients were examined to confirm the type of anemia due to erythrocyte morphology and to exclude other pathologies such as leukemia**.**

Overt hypothyroidism diagnosis was made when elevated TSH and low levels of free T4 and/or free T3 were observed. Subclinical hypothyroidism was defined as an elevated Serum TSH with normal free T4 and free T3 levels.

Anemia is defined as hemoglobin levels lower than12 g/dL in women and 13 g/dL in men. Iron deficiency anemia is defined as serum Fe levels lower than 60 µg /dL, iron binding capacity greater than 215 µg /dL, ferritin levels lower than10 ng/dL and with microcytosis and hypochromia in peripheral blood smear. Folic acid deficiency anemia is defined as folic acid levels lower than 3ng/mL together with macrocystosis in peripheral blood smear. Vitamin B12 deficiency anemia is defined as B12 levels lower than 211 pg/mLwith increased MCV levels and with macrocystosis in peripheral blood smear. Anemia of chronic disease is defined as low Iron, low iron binding capacity and ferritin levels normal or elevated with normal folic acid and vitamin B12 levels.

Statistical analyses were carried out using SPSS 16 Software to indicate the degree of significant between the mean values of the patient groups and the mean values of the corresponding controls. Descriptive data were given as mean ± standard deviation (SD), with p values less than 0.05 as statistically significant. Pearson correlation test was used in correlations between parametric variables.

RESULTS

Demographic characteristics and biochemical values of patient and control groups participating in this study are shown in Table 1.

In our study, anemia was reported in 111 of 231 cases (48.05%) and in 59 of 209 (28%) controls and the difference between two groups was statistically significant ($p < 0.001$). Anemia was found in 46.8% of sub-clinical hypothyroidism cases and 49.3% of overt hypothyroidism cases. There was no statistical difference in terms of anemia frequency between Sub-clinical and overt hypothyroid groups (p=0.593). However, anemia frequency was statistically significant for subclinical and overt hypothyroid groups compared to the Controls (p=0.018 and p=0.0003 respectively).

Biochemical data of the patients with anemia in hypothyroid and control groups are shown in Table-2. Anemia was present in 53 of 108 overt hypothyroid cases, 58 of 123 sub-clinical hypothyroid cases and 59 of 209 controls. There was no statistical difference between hematocrit, hemoglobin, Ferritin, vitamin B12 level, folic acid and iron levels in the patients with anemia.

The etiologies of anemia in patients and controls are shown in Table-3. In overt and sub-clinical hypothyroid patient groups, anemia of chronic disease frequency was found to be the most common type. It was present in 69 of 231(30%) of patient groups.

Microcytic anemia was seen in 8.3% of overt hypothyroid patients and in 7.1% of subclinical hypothyroid patients. The frequency of macrocytic anemia was 8% in overt hypothyroid patients and 13% in

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subclinical hypothyroid patients. There was normocytic anemia in 33% of overt hypothyroid patients and in 26.7% of subclinical hypothyroid patients.

Table 1: Clinical and Laboratory data of Patients of all the Groups

	Subclinical Hypothyroidism	Overt hypothyroidism	Control group	P value
Number	123	108	209	
Gender (M/F)	16/107	14/94	33/176	
Age (years)	48.11±12.25	48.35 ± 11.78	36.87 ±17.82	
TSH (0.3-5.0 mIU/ml)	11.43 ± 7.62	56.96 ± 30.34	2.3 ± 1.7	0.000
FT3 (3.5 - 6.5 pmol/L)	4.18 ± 0.59	1.7±0.94	4.96 ± 0.84	0.000
FT4 (10 –23 pmol/L)	13.35 ± 3.61	6.43± 2.72	14.11± 2.83	0.000
Hemoglobin (g/dl)	12.71 ± 1.57	11.31 ± 1.66	13.27 ± 1.14	0.000
Hematocrit (37-52%)	37.71 ± 3.50	36.20 ± 4.05	40.35 ± 2.33	0.002
S.Iron (60-180 µg/dl)	63.85 ± 16.77	61.86 ± 18.64	99.82± 16.76	0.000
Iron binding capacity (215-535 µg/dl)	229 ± 93.64	220 ± 104.78	241± 44.09	0.178
Ferritin (10-300 ng/ml)	94 ± 30	104 ± 38	99 ± 23	0.728
Vit.B12 (211-911 pg/ml)	393 ± 99	327 ± 91	412 ± 93	0.001
Folic acid (3-20 ng/ml)	8.2 ± 3.4	7.97 ± 3.9	9.1 ± 3.8	0.025

Table 2: Laboratory values of the anemic patients in all groups

Parameter	Subclinical Hypothyroidism n=58	Overt Hypothyroidism n=53	Control Group n=59	P value (<0.05)
Hemoglobin (g/dL)	10.9 ± 1.7	10.5 ± 1.5	11.2 ± 1.3	0.52
Hematocrit (%)	32.7 ± 3.5	32.6 ± 4.1	32.3 ± 2.5	0.80
Vitamin B12 (211-911pg/ml)	319.7 ± 229.6	418.9 ± 392.3	345.6 ± 293.4	0.32
Folic acid (3-20 ng/mL)	7.7 ± 3.1	7.9 ± 4.9	8.6 ± 3.9	0.51
Iron (60-180 µg/dl)	63.3 ± 32.1	56.4 ± 31.9	57.6 ± 27.6	0.38
Ferritin (10-300 ng/mL)	28.5 ± 37.3	40.9 ± 66.1	31.8 ± 34.6	0.39

Table 3: Etiology and percentages of Anemia in overt and sub-clinical hypothyroidism

Type Of Anemia	Overt Hypothyroidism n=108	Sub-clinical Hypothyroidism n=123
Iron deficiency anemia	8.3%	7.1%
Folate deficiency anemia	4%	6.4%
B12 deficiency anemia	4%	6.6%
Anemia of chronic disease	33%	26.7%

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DISCUSSION

According to the WHO data, anemia prevalence is 24.8% throughout the world and it is seen more frequently in underdeveloped countries [10]. Anemia is a severe public health problem in India, which may be precipitated by conditions such as hypothyroidism. In order to carry out the treatment of the patient with anemia correctly, it is necessary to determine etiological cause. The adverse effect of hypothyroidism on the hematological system can be anemia development. In our study, we examined this relationship of hypothyroidism (overt and subclinical) with anemia. In our study, anemia frequency in overt and subclinical hypothyroid groups was found to be 49.3% and 46.8%, respectively. Anemia frequency in patients with overt and subclinical hypothyroidism was found to be statistically significant when compared to control group (p=0.000). This result gave rise to thought that hypothyroidism presence may be a risk factor in anemia development.

Our results are in agreement with that of the studies done by Bamashmous S.A. et al [11] and Erdogan Mehmet et al [12]. They reported anemia of chronic disease as the most frequent type of anemia and our results also found anemia of chronic disease as the commonest type.

Development of erythroid colony is stimulated directly or indirectly by thyroid hormones. The deficiency of thyroid hormones leads to the abnormal erythroid colony which affects oxygen distribution to tissues. Diminution of erythroprotein level in the absence of thyroid hormones causes normocytic anemia and therefore it is the most frequent type of anemia in hypothyroid patients [13]. The observation made by Christ-Crain and colleagues indicated that erythropoietin values were increased as result of levothyroxine treatment in women with subclinical hypothyroidism [14].

The prevalence of vitamin B12 deficiency increases along with the age and Framingham study reveals that the prevalence in old population is 12%. Erdogan Mehmet and his colleagues [12] reported the prevalence of macrocytic anemia as 10% and 11% in overt and sub-clinical hypothyroid cases respectively. Bamashmous S.A. and colleagues [11] reported prevalence of macrocytic anemia as 8% and 13.4% respectively in overt and subclinical-hypothyroid cases.

In our study the frequency of macrocytic anemia was 8% and 13% in overt and sub-clinical hypothyroid cases respectively and these results are in agreement with the before mentioned studies. Macrocytic anemia occurs as a result of deficiency of either vitamin B12 or Folic acid or both. Vitamin B12 deficiency mostly occurs as a result of malabsorption due to pernicious anemia accompanying hypothyroidism. Antibodies against gastric parietal cells were determined in 1/3 of the patients with primary hypothyroidism. In the study carried out by R Carnel, et al [17], thyroid disorder and hypothyroidism were determined respectively in 24.1% and 11.7% of the patients with pernicious anemia. Insufficient intake, absorption change arising from deceleration in intestinal motility, intestinal wall edema, and bacterial infiltration are blamed among other reasons causing vitamin B12 deficiency in hypothyroidism. In our study vitamin B12 deficiency was found in 5.3% of the cases [15, 16].

Folic acid deficiency, one of the reasons of anemia, occurs as a result of intestinal malabsorption. Again hypothyroidism ruins folate mechanism by decreasing hepatic level of dihydrofolate reductase such as methylene-tetrahydrofolate reductase. Folic acid deficiency almost always occurs as secondary to an underlying disease [4]. In our study folate deficiency was found in 5.2% of the cases.

Iron deficiency is one of the commonest causes of anemia in India. The various causes include insufficient intake, hookworm infestation menstrual loss in females etc. In our study, iron deficiency anemia was found in 7.7% in hypothyroid patients. Malabsorption and iron deficiency anemia depending on menorrhagia occurring as a result of various hormonal instability are observed in hypothyroidism [12]. In a study carried out by Cinemre H. and colleagues, they showed that the efficacy and absorption of oral iron treatment in women with subclinical hypothyroidism improved after levothyroxine supplementation. This demonstrates that hypothyroidism should be assessed in patients with anemia [9].

Hypothyroidism is a common endocrinal disorder affecting the people of our society. Anemia which is already prevalent in our society may be further influenced by Sub-clinical and Overt hypothyroidism. Therefore, determination of etiological reasons of anemia and arrangement of the treatment is important [12].

We found an elevated anemia frequency in hypothyroid patients consistent with the literature. We also reported that the most frequent cause was linked to anemia of chronic disease. Further studies covering larger population are needed to substantiate this increased association of anemia in hypothyroidism.

CONCLUSION

Anemia of chronic disease is the most common type of anemia in hypothyroid patients. Therefore, suspicion of hypothyroidism should be considered in anemias with uncertain etiology.

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