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FREQUENCY OF HYPOTHYROIDISM AND SUB-TYPES IN PATIENTS OF THALASSEMIA MAJOR ON CHELATION THERAPY

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Abstract

Objective: *To study frequency of hypothyroidism and clinical associations in transfusion dependent patients of thalassemia major on chelation therapy*

Study Design: *Analytical cross-sectional study*

Place and Duration of Study: *Pediatrics department of Combined Military Hospital, Sialkot from January 2024 – June 2024*

Methodology: *A total of 320 patients were included in the final study protocol. Laboratory investigations carried out in all patients included blood complete picture, serum ferritin levels, thyroid profile including thyroid stimulating hormone (TSH) and free T4 levels to determine presence of absence of hypothyroidism and its sub-types. Primary variables studied were frequency of hypothyroidism and its sub-types. Secondary variables included relationship between number of transfusions with severity of thyroid disease*

Results: *Serum ferritin levels between sub-clinical and overt hypothyroidism were less than 2000 mg/ml in 24 (8.0%) versus 00 (0%) patients, between 2000-3000 mg/ml in 30 (10.0%) versus 00 (0%) patients, between 3000-4000 ng/ml in 186 (61.8%) versus 00 (0%) patients, and more than 4000 ng/ml in 61 (20.3%) versus 19 (100%) patients (p<0.001). Duration of transfusion between both groups showed duration of less than 5 years in 24 (8.0%) versus 00 (0%) patients, 5-10 years in 238 (79.1%) versus 02 (10.5%) patients and more than 10 years in 39 (13.0%) versus 17 (89.5%) patients (p<0.001).*

Conclusion: *Frequency of hypothyroidism sub-type showed sub-clinical hypothyroidism in 301 (79.7%) patients while overt hypothyroidism was found in 19 (5.9%) of patient and are the major sub-type associated with patients on prolonged chelation therapy linked with duration of blood transfusions and levels of ferritin in transfusion dependent thalassemia major pediatric patients.*

INTRODUCTION

Thalassemia major is one of the commonest hereditary conditions in the pediatric age group. [1] It follows an autosomal recessive pattern of inheritance, and the reported prevalence worldwide is 3-4% with increased prevalence reported in Middle East, Southeast Asia and the Mediterranean. In Pakistan, the reported prevalence is more than 10,00,000 with 5000-9000 cases being diagnosed each year. [2] The reported increased prevalence in specific geographical areas is due to the increased carrier rate

in both parents with the major reported cause being consanguineous marriages. It is a structural disorder of the globin chains in the hemoglobin structure resulting in quantitative defect of the molecule. This results in abnormal production of globin chains resulting in destruction of red blood cells leading to anemia. [3] The affected globin chains and their number of mutations classifies the severity of the disease into thalassemia major and minor. Patients with thalassemia major presents very early in life with severe anemia requiring lifelong blood transfusion of maintain levels of hemoglobin necessary for adequate oxygen transport in the body. [4]

The complications of routine transfusions are multiple with iron overload being the most common in these patients. Multiple transfusions hamper the normal mechanism of the body to excrete the excess iron since the rate of elimination is less than the amount being given through blood transfused. [5] The excess iron is deposited in the tissue most notably of the endocrine system. Studies have reported that after hypogonadism, hypothyroidism is the major abnormality seen in these patients due to iron deposition affecting the normal functioning of the thyroid gland. [6] The reported prevalence internationally is from 5.6-17% of all patients with thalassemia. [7] This results in metabolic complications including low weight, failure to thrive and poor growth. Since transfusion dependency cannot be eliminated in these patients, iron chelation is done routinely to excrete excess iron from the body. [8]

The pediatric age group is especially prone to the complication of hypothyroidism but local studies of disease prevalence and association of thalassemia with hypothyroidism on clinical outcomes is scarce in this group of patients. We aim to carry out this study to report the frequency of hypothyroidism and its sub-types and also study factors affecting the clinical outcome and disease complications in these patients.

METHODOLOGY

This cross-sectional study was carried out at the Pediatrics department of Combined Military Hospital, Sialkot from January 2024 – June 2024, after approval form the ethical review board vide letter no. (ERC 19/2024). The sample size was calculated keeping the confidence interval at 95%, margin of error at 5%, with the reported population prevalence of thalassemia major patients with hypothyroidism being 26.8%.[9] Minimum sample size using the WHO calculator came out to be 301 patients. We included 320 patients in the final study protocol.

Inclusion criteria included male and female pediatric patients between ages 4-18 years of age diagnosed with thalassemia major, on chelation therapy due to multiple transfusions

Exclusion criteria included patients with already established thyroid disease, patients already on thyroid replacement therapy, patients with malignancy, patients lost to follow-up and non-consent of parents or next of kin to be included in the study

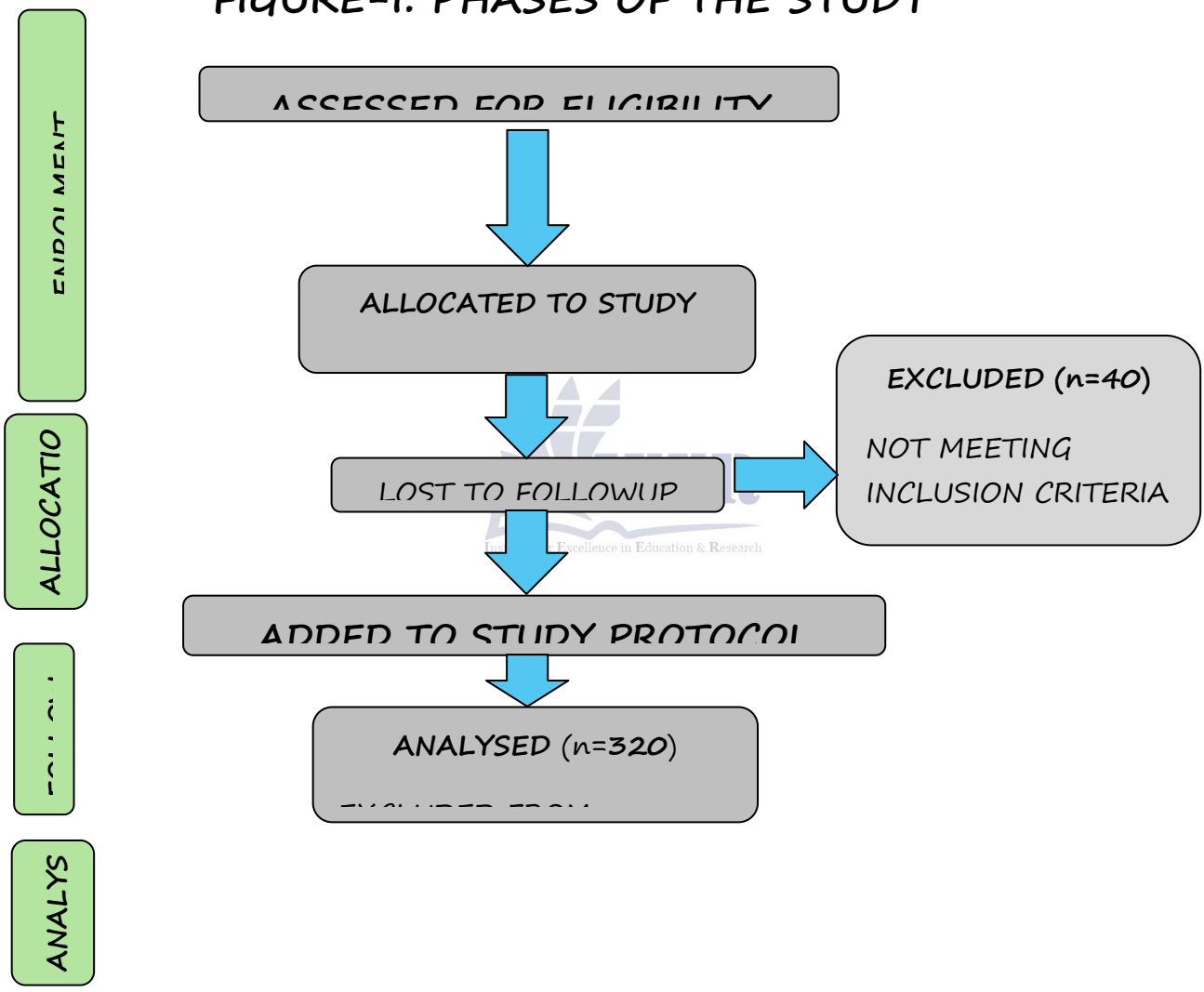
The study method included all patients as per the inclusion criteria furnished. The parents of the children were thoroughly informed and counseled regarding the study procedure but not the outcome variables and were requested for routine follow-up after investigations as per the study design. A written informed consent was taken from all patients for inclusion in the study. All patients were diagnosed cases of thalassemia major confirmed using hemoglobin electrophoresis using high performance liquid chromatography (HPLC).

Demographic data of all patients included in the study protocol was endorsed by a resident pediatrics unaware of the study protocol, on a proforma provided by the study team including age, weight, gender, duration of disease, frequency of blood transfusion per month and in the last 12 months, history of splenectomy, neck swelling and family history of thyroid disorder. Laboratory investigations carried out in all patients included blood complete picture, serum ferritin levels, thyroid profile including thyroid stimulating hormone (TSH) and free T4 levels to determine presence of absence of hypothyroidism and its sub-types. Sub-clinical primary hypothyroidism was defined as increased level of serum TSH levels above 4.49 mIU/L with normal levels of serum T4 levels (5-12 mcg/dl) in the body. Overt hypothyroidism was defined as increased level of serum TSH levels above 4.49 mIU/L and serum T4 levels more than 12mcg/dl. All laboratory

investigations were collected by a resident pediatrics unaware of the study protocol and were handed over to the statistical department for further analysis. Primary variables studied were frequency of hypothyroidism and its sub-types. Secondary variables included relationship between number of transfusions with severity of thyroid disease

Demographic data were statistically described in terms of mean and SD, frequencies, and percentages when appropriate. Frequency variables were compared using the Chi-square test while mean values were compared using the independent samples t-test. A p value of ≤ 0.05 was considered statistically significant. All statistical calculations were performed using Statistical Package for Social Sciences 26.0.

FIGURE-1: PHASES OF THE STUDY



RESULTS

A total of 360 patients were assessed for eligibility and 320 patients meeting the inclusion criteria were added into the study protocol. Mean age of patients in the study group was 8.79 ± 2.54 years and mean weight was 18.73 ± 3.26 kg. Gender distribution revealed 261 (81.6%) males and 59 (18.4%) females. Mean age at which thalassemia major was diagnosed was 2.02 ± 0.58 years. Neck swelling on examination was found in 104 (32.5%) patients. Family history of thyroid disease was found in 54 (16.9%) patients while history of thalassemia in the family was positive in 248 (77.5%) patients. Splenectomy was done in 255 (79.7%) patients in the study group. Frequency of hypothyroidism sub-type in the study group showed sub-clinical hypothyroidism in 301 (79.7%)

patients while overt hypothyroidism was found in 19 (5.9%) of patients. Transfusion history showed duration since transfusion were being done was less than 5 years in 24 (7.5%) patients, 5-10 years in 240 (75.0%) patients while it was being done for more than 10 years in 56 (17.5%) patients (Table-I).

Laboratory parameters between sub-clinical versus overt hypothyroidism sub-types showed mean levels of hemoglobin being 5.95 ± 0.98 h/dl versus 5.79±1.27 g/dl (p=0.492), mean hematocrit values being 19.53 ± 1.49 versus 19.74 ± 1.48 (p=0.568), mean ferritin levels being 3524.11±765.73 mcg/ml versus 4499.79 ± 168.04 mcg/ml (p<0.001), mean serum TSH levels being 17.55±5.29 mIU/L versus 15.95±5.30 mIU/L between both groups (p=0.201) and mean serum T4 levels being 8.26±1.21 mcg/dl versus 19.79 ± 1.98 mcg/dl between both groups (p<0.001). Co-relation between ferritin levels and duration of transfusion showed that serum ferritin levels between sub-clinical and overt hypothyroidism were less than 2000 mg/ml in 24 (8.0%) versus 00 (0%) patients, between 2000-3000 mg/ml in 30 (10.0%) versus 00 (0%) patients, between 3000-4000 ng/ml in 186 (61.8%) versus 00 (0%) patients, and more than 4000 ng/ml in 61 (20.3%) versus 19 (100%) patients (p<0.001). Duration of transfusion between both groups showed duration of less than 5 years in 24 (8.0%) versus 00 (0%) patients, 5-10 years in 238 (79.1%) versus 02 (10.5%) patients and more than 10 years in 39 (13.0%) versus 17 (89.5%) patients (p<0.001) (Table-II).

TABLES

TABLE-I: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS (n=320)

VARIABLE	STUDY GROUP (n=320)
MEAN AGE (YEARS)	8.79±2.54
MEAN WEIGHT (KGS)	18.73±3.26
GENDER DISTRIBUTION	
• MALE	261 (81.6%)
• FEMALE	59 (18.4%)
MEAN AGE OF THALASSEMIA MAJOR DIAGNOSIS (YEARS)	2.02±0.58
HISTORY OF NECK SWELLING	104 (32.5%)
FAMILY HISTORY OF THYROID DISEASE	54 (16.9%)
FAMILY HISTORY OF THALASSEMIA	248 (77.5%)
SPLENECTOMY	255 (79.7%)
FREQUENCY OF HYPOTHYROIDISM SUB-TYPES	
• SUB-CLINICAL HYPOTHYROIDISM	301 (79.7%)
• OVERT HYPOTHYROIDISM	19 (5.9%)
DURATION OF TRANSFUSIONS (YEARS)	
• LESS THAN 5 YEARS	24 (7.5%)
• 5-10 YEARS	240 (75.0%)
• MORE THAN 10 YEARS	56 (17.5%)

TABLE-III: CO-RELATION OF CLINICAL VARIABLES WITH HYPOTHYROIDISM SUB-TYPES (n=320)

VARIABLE	SUB-CLINICAL HYPOTHYROIDISM (n=301)	OVERT HYPOTHYROIDISM (n=19)	p VALUE
MEAN HEMOGLOBIN (G/DL)	5.95±0.98	5.79±1.27	**0.492**
MEAN HEMATOCRIT (%)	19.53±1.49	19.74±1.48	**0.568**
MEAN SERUM FERRITIN LEVELS (MCG/ML)	3524.11±765.73	4499.79±168.04	**<0.001**
MEAN SERUM TSH (mIU/L)	17.55±5.29	15.95±5.30	**0.201**
MEAN SERUM T4 (MCG/DL)	8.26±1.21	19.79±1.98	**<0.001**

SERUM FERRITIN LEVELS			
• <2000 NG/ML	24 (8.0%)	00 (0%)	<0.001
• 2000-3000 NG/ML	30 (10.0%)	00 (0%)	
• 3000-4000 NG/ML	186 (61.8%)	00 (0%)	
• >4000 NG/ML	61 (20.3%)	19 (100%)	
DURATION OF TRANSFUSION			
• <5 YEARS	24 (8.0%)	00 (0%)	<0.001
• 5-10 YEARS	238 (79.1%)	02 (10.5%)	
• >10 YEARS	39 (13.0%)	17 (89.5%)	

DISCUSSION:

The study was carried out to not only report the frequency of hypothyroidism in pediatric group with thalassemia major, but also to co-relate the clinical variables with the disease. Our study concluded a strong causal relation between iron overload and thyroid disease. It is reported that hypoxia, liver dysfunction and immune factors play a key role in deposition and destruction of thyroid gland in these patients. [10] The mean age in our study group was 9 years with the age of diagnosis being 2-3 years. This is corroborated with international and national studies done by Donze et al and Batool et al, both of which also reported the age range of diagnosis between 2-3 years. [11, 12] Acka et al concluded that more than 80% of pediatric patients undergo splenectomy between the ages of 5-8 years when the spleen becomes enlarged due to consistent destruction of abnormal red blood cells. [13] This is in line with results of our study as well where 80% of the pediatric population had already undergone splenectomy. A strong family history with more than 80% of the patients giving a positive history of their parents, siblings or first-degree relatives suffering from thalassemia. As already mentioned, consanguineous marriages in the country are one of the major reasons why this reported prevalence is so high and requires more robust programs to discourage the practice especially in our country. [14]

When assessing the frequency of hypothyroidism sub-types, we found that more than 85-92% of pediatric patients had sub-clinical form of the disease, while 5-7% were reported to be suffering from overt sub-type. This is in line with international literature reporting prevalence rates of over hypothyroidism between 5-7% of all cases of hypothyroidism by studies done by Sriwichakorn et al and a meta-analysis done by Haghpanah et al. [15, 16] When reporting the duration of transfusions in the study groups, more than 75% of the patients were receiving regular transfusions for the last 5-10 years. This is because the mean age of diagnosis was around 2-3 years and patients enrolled has a mean age of 9 years with a range from 3-14 years of age. When comparing and co-relating laboratory variables with the two sub-types of hypothyroidism reported in the group, we found no statistically significant difference in the values of hematological variables including hemoglobin and hematocrit between the two sub-types but found a significant difference in the values of ferritin which show that higher levels are clinically co-related with more severity of the disease which is expected as the greater the amount of iron in the body, the greater the chance of severe damage to the thyroid gland. This is also supported by the results of studies done, showing a linear co-relation between ferritin levels and severity of thyroid disease. [17]

We also found a strong co-relation between serum ferritin levels and patients presenting with more serve sub-type of the disease. In our study, subclinical hypothyroidism showed range of serum ferritin levels between 2000-4000 ng/ml whereas in overt sub-type the levels of ferritin were above the 4000 ng/ml threshold with a strong statistical difference int eh values between both groups. This finding is in line with local study done by Saleem et al at Rahim Yar Khan which also reported similar findings with respect to age of diagnosis, percentage of sub-clinical, overt sub-type and relation with disease severity and ferritin levels. [18] Also to be noted was the link between duration of transfusions and thyroid disease with almost all patients with overt disease having had transfusion for more than 10 years. These two findings of ferritin levels and duration of transfusion therapy should help clinicians segregate patients with suspicion of clinical hypothyroidism and form

treatment guidelines accordingly including robust thyroid testing and starting therapy as soon as possible with thyroid replacement to prevent complications.

RECOMMEDATIONS

The study recommends using high serum ferritin levels and prolonged duration of transfusions are good predictors of severe thyroid function in pediatric patients and to start treatment regimens accordingly

CONCLUSION:

Frequency of hypothyroidism sub-type showed sub-clinical hypothyroidism in 301 (79.7%) patients while overt hypothyroidism was found in 19 (5.9%) of patient and are the major sub-type associated with patients on prolonged chelation therapy linked with duration of blood transfusions and levels of ferritin in transfusion dependent thalassemia major pediatric patients.

LIMITATIONS

The limitations are that the study is single center only.

CONFLICT OF INTEREST:

None.

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