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Clinico hematological profile in cases of hereditary hemolytic anemia in a tertiary care hospital.

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Abstract

Aim: To study the clinical and hematological correlation in the cases of hereditary hemolytic anemia.

- Study design: Cross sectional observational study
- Place and duration of the study:_This Study was carried out at a tertiary care centre; over a period of 24 months from August 2020 to July 2022.

Introduction: Hemolytic anemia is a disorder that occurs when red blood cells are destroyed faster than they can be replaced. It can develop quickly or slowly and it can be mild or serious.

Methodology: All the newly diagnosed cases as well as previously diagnosed cases of hereditary hemolytic anemia having evidence of hemolysis were included in this study. After taking informed written consent of patient in adults and parent's /guardian in pediatric age group, the patients having indicative symptoms of hemolytic anemia were studied further. A total of 40 cases of hemolytic anemia were studied.

Inclusion Criteria

• All the newly diagnosed cases of hereditary hemolytic anemia as well as known cases on follow up were included in this study.

• Cases having significant, indicative history and evidence of hemolysis either intravascular or extra vascular type were included in the study.

• Cases of all ages and sex were included in the study.

Exclusion Criteria

• Patients with anemia of etiology other than hemolysis like nutritional cause, hematopoietic malignancies,

metastasis in bone marrow of other malignancies, aplasia of bone marrow and acquired hemolytic anemia were excluded from the study.

• Patients having clinical evidence but no laboratory evidence of hemolytic anemia were excluded from the study.

Results: Of the 40 cases of hereditary hemolytic anemia, 33 cases (82.5%) of beta thalassemia major, 5 cases (12.5%) of beta thalassemia trait, and 1 case (2.5%) of sickle cell anemia and hereditary spherocytosis each were identified. More than half of the cases (57.5%) gave history of consanguineous marriage; out of which 2nd degree marriage was observed to be the most common (45%).

Conclusion: Although many hemolytic disorders cannot be cured, these can be prevented by increased awareness, which can lead to the detection of the carrier condition, genetic counselling, premarital/prenatal counselling and antenatal diagnosis, all of which may assist to lower the prevalence.

Keywords: hereditary, hemolytic anemia, hemolytic facies.

Introduction

Anemias such as hemolytic anemias occurs when the bone marrow's ability to produce new red blood cells is exceeded by an increased rate of red cell destruction. Red blood cells are abnormally breaking down, either extra vascularly or intravascularly. (1) Due to the fact that a number of subtypes can be acquired or congenital, hemolytic anemias in general affect people of all ages, races, and genders.

All individuals with unexplained normocytic or macrocytic anemia should take it into consideration because it ranges in severity from chronic to life-threatening. (2).

The most frequent clinical manifestations of hemolytic anemia, in addition to anemia/weakness/pallor includes intermittent jaundice, splenomegaly, hepatomegaly, thalassemic facies, gall stones, hemolytic facies, growth retardation, and edema. (3) When hemolysis is a concern, a peripheral blood smear should be analyzed and aberrant cells should be looked for. (4) A thorough evaluation of hemolytic anemia should be performed for specific typing but doing so is viewed as a great burden in India because the majority of individuals live in poor socioeconomic strata. To categorize or type hemolytic anemia and provide guidance for additional testing, a basic panel of tests would be quite helpful. The basic panel of tests, which includes the complete blood count (CBC), peripheral smear study, serum bilirubin, serum ferritin, urobilinogen, hemoglobinuria, and hemosiderin Uria, will help to determine the presence of hemolytic anemia.

These tests also point in the right direction for more specialized tests, such as the Coomb's test, hemoglobin electrophoresis, sickling test, osmotic fragility test, and d-dimer. We chose this subject for the study because, despite the fact that the sickness is rather common, there aren't many studies specifically on this topic in this region of the country, according to a review of the literature.

Although these problems cannot be cured, they can be averted if the medical community raises awareness of them, leading to the detection of the carrier state, genetic counselling, and antenatal diag nosis. Additional findings from this study will add to the information already in the data. So, in such situations of hemolytic anemia, we intended to research the asso ciation between the clinical and hematological profiles.

Materials and methods

Material

1) Automated hematology analyzer (NIHON KOHDEN) - 5 part

2) Slides: Clean grease free slides

3) Various laboratory reagents required for the test procedures

Method

1. All the newly diagnosed cases as well as old diagnosed cases of hereditary hemolytic anemia having evidence of hemolysis were considered in this study.

2. After taking informed written consent of patient in adults and parent's /guardian in pediatric age group, the patients possessing indicative symptoms of hemolytic anemia were examined.

Clinical Workup

All clinical details of the patients were documented from them in person as per proforma including detailed history, age, sex, religion, blood group, socio economic status, physical examination like presence of pallor, icterus, hemolytic facies, anthropometric measurements, family history, consanguinity, history of co morbid conditions like diabetes, hypertension, autoimmune disease and prosthetic valve, history of blood trans fusion, organomegaly like hepatomegaly, splenomegaly.

Investigations –

Following tests were performed to type the hemolytic anemia-

▪ Routine investigations like CBC including all the red cell indices (Hemoglobin, TLC, RBC count, WBC count, Platelet count, PCV, MCV, MCH, MCHC, RDW), peripheral blood smear examination, reticulocyte count, rapid malarial test, serum bilirubin, serum ferritin, Hb electrophoresis.

▪ Special investigations like osmotic fragility test, G6PD screening test, Sickling test, coomb's test, d-dimer.

▪ Urine routine and tests for urobilinogen, hemoglobin Uria and hemosiderin Uria

Ultra sonographic findings like organomegaly, gall stones or any other abnormalities will be noted. X-ray skull to rule out bony abnormalities like Crew cut appearance, CT scan were also considered.

To identify the etiology of hemolytic anemia and to correlate it to the patient's clinical and hematological characteristics, a thorough investigation into each of these cases was conducted.

The blood and urine samples were collected and labelled for further investigations.

Cases were classified as hereditary hemolytic anemia on the basis of age, gender, family history, outcomes of con sanguineous marriage, clinical features, Hemato logical and biochemical findings and certain special tests like hemoglobin electrophoresis.

Results and discussion

Results

A cross sectional observational study consisting of 40 cases attending tertiary care center for follow ups as already diagnosed cases of hereditary hemolytic anemia or newly diagnosed cases were undertaken to find clinical and hematological correlation.

Table 1: Distribution according to different types of hereditary hemolytic anemia in the present study (n=40)

	Types of hemolytic anemia	No.	%
Hereditary (n=40)	Beta thalassemia major	33	82.5
	Beta thalassemia trait	5	12.5
	Sickle Cell Anemia	1	2.5
	Hereditary spherocytosis	1	2.5

- Amongst 40 hereditary hemolytic anemia cases, 33 cases (82.5%) were of beta thalassemia major, 5 cases

(12.5%) of beta thalassemia trait and 1 case (2.5%) each of sickle cell anemia and hereditary spherocytosis.

Table 2: Age wise distribution in different types of hereditary hemolytic anemia in the present study (n=40)

	Up to 1 year	1-15 years	16-30 years	31-45 years	>45 years
	%	%	%	%	%
Hereditary (40)					
Beta thalassemia major	3 (9.1%)	25 (75.7%)	5 (15.1%)	0	0
Beta thalassemia trait	0	1 (20%)	1 (20%)	3 (60%)	0
Sickle Cell Anemia	0	0	0	1 (100%)	0
Hereditary spherocytosis	0	1 (100%)	0	0	0

Amongst hereditary hemolytic anemia,

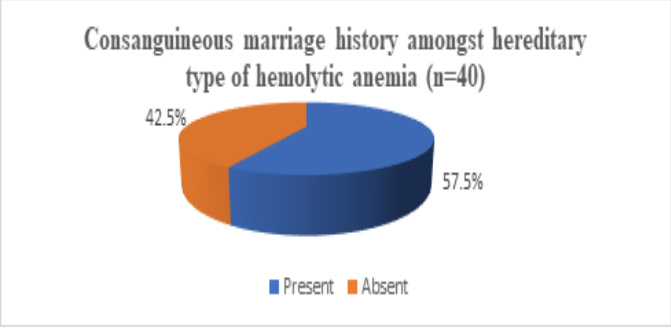
- It shows that maximum number of cases were seen in 1 to 15 years of age group consisting 25 cases (75.7%) of beta thalassemia major
- Beta thalassemia trait showed maximum number of cases in 31- 45 years of age group consisting of 3 cases (60%).

Table 3: Gender wise distribution of study subjects having hemolytic anemia (n=40)

Gender	No.	%
Male	27	67.5
Female	13	32.5

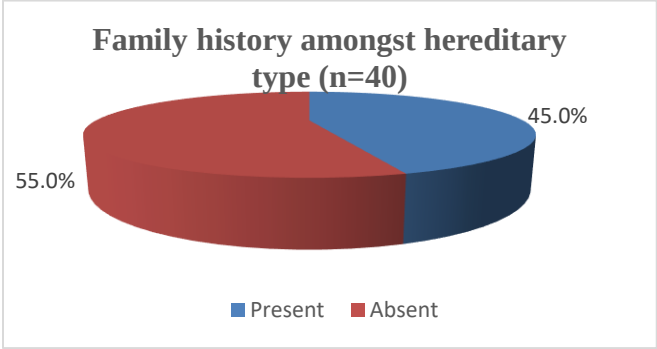
- The study had 27 (67.5%) male patients and 13 (32.5%) female patients with different types of hemolytic anemia.
- It is noted that there is male preponderance in the study with male to female ratio of 2:1.

Figure 1: Pie chart showing distribution on the basis of consanguineous marriage history amongst hereditary type (n=40)



- History of consanguineous marriage of parents were present in 23 (57.5%) cases.
- Other members of family were not affected by either similar or any other illness.

Figure 2: Pie chart showing distribution on the basis of family history amongst hereditary type (n=40)



The study showed 18 (45%) cases having positive family history out of total 40 (42.1%) cases of hereditary hemolytic anemia.

Table 4: Clinical features in hereditary type of hemolytic anemia (n=40)

Type of hemolytic anemia	Total number of cases	Anemia/ Pallor	Weakness, failure to thrive	Hemolytic facies	Jaundice/ Icterus	Growth retardation	Hepatomegaly	Splenomegaly
	%	%	%	%	%	%	%	%
Beta thalassemia major	33	33 (100%)	20 (60.6%)	22 (66.7%)	25 (75.7%)	22 (66.6%)	33 (100%)	33 (100%)
Beta thalassemia trait	5	4 (80%)	2 (40%)	0	0	0	0	0
Sickle Cell Anemia	1	1 (100%)	1 (100%)	1 (100%)	0	0	1 (100%)	1 (100%)
Hereditary spherocytosis	1	1 (100%)	0	0	1 (100%)	0	0	1 (100%)

- Most common presentation next to pallor was jaundice/ icterus (75.7%). Mild to moderate hepato megaly and splenomegaly was noticed.
- Growth retardation and hemolytic facies characterised by frontal bossing, depressed nasal bridge, prominent malar eminence, crowded teeth were seen in 66.7% cases.

Table 5: Hematological findings in different types of Hereditary hemolytic anemia (n=40)

Type of hemolytic anemia	Hb		MCV		MCH		MCHC		RDW		Reticulocyte Count	
	Mean ±SD	Range	Mean ±SD	Range	Mean ±SD	Range	Mean±SD	Range	Mean ±SD	Range	Mean ±SD	Range
Beta thalassemia major	6.56 ±1.90	2-9.4	59.51 ±5.54	50-70	17.48 ±2.62	13-25	29.36 ±1.46	27-32	14.16 ±0.63	13-15.9	1.9 ±0.26	1.4-2.8
Beta thalassemia trait	10.4 ±2.24	10-12	72.16 ±5.51	65-80	23.6 ±2.14	20-25	30.66 ±1.31	29-33	14.5 ±0.66	13.8-15.3	2.56 ±0.84	1.9-4
Sickle Cell Anemia	6	-	75.8	-	24.2	-	32	-	16.2	-	3.0	-
Hereditary spherocytosis	12	-	80	-	29	-	37	-	18	-	5	-

- The mean values of RBC indices in beta thalassemia major were Hb – 6.56, MCV – 59.5, MCHC – 29.3, RDW – 14.1 and reticulocyte count in the range of 1.4 - 2.8.

- The mean values of RBC indices in beta thalassemia trait were Hb – 10.4, MCV – 72.1, MCHC – 30.6, RDW – 14.5 and reticulocyte count in the range of 1.9 - 4.
- The hemoglobin of patient of sickle cell anemia was 6 g% while of hereditary spherocytosis was 12 g%.

Table 6: Biochemical findings in different types of hemolytic anemia (n=95)

Type of hemolytic anemia	Total Serum Bilirubin		Direct Bilirubin		Indirect Bilirubin		Serum Ferritin	
	Mean ±SD	Range	Mean ±SD	Range	Mean ±SD	Range	Mean ±SD	Range
Congenital (40)								
Beta thalassemia major	3.81 ±0.94	2.4-6.8	1.76 ±0.48	1-2.8	2.05 ±0.57	1.1-4.0	1384.12 ±101.52	1200-1564
Beta thalassemia trait	2.1 ±0.33	1.7-2.5	0.96 ±0.39	0.6-1.6	1.14 ±0.20	0.9-1.4	269 ±75.35	150-350
Sickle Cell Anemia	3	-	1.4	-	1.6	-	1468	-
Hereditary spherocytosis	2	-	0.7	-	1.3	-	200	-

- Hyperbilirubinemia is seen in all the types of hemolytic anemia and high serum ferritin levels are seen in beta thalassemia major and sickle cell anemia.

Table 7: Urobilinogen status in study subjects of hemolytic anemia (n=40)

Type of hemolytic anemia	Positive	%
Thalassemia Major	30	75
Hereditary Spherocytosis	1	2.5
Total	31	77.5

Out of 40 cases; 31 cases (77.5%) showed positive urobilinogen status.

Table 8: Hemoglobinuria and Hemosiderin Uria status in study subjects of hemolytic anemia (n=40)

Type of hemolytic anemia	Hemoglobinuria Positive	Hemosiderin Uria positive
Thalassemia Major	10	5
Percentage	30%	15%

- Out of 40 cases; 10 cases (30%) were positive for hemoglobinuria
- Out of 40 cases; 5 cases (15%) were positive for hemosiderin Uria.

Table 9: Hemoglobin electrophoresis status in the study objects of hemolytic anemia (n=40)

Type of hemolytic anemia	No.	%
Thalassemia Major	33	100
Sickle Cell Anemia	1	100
Total	34	85

Out of 40 cases; HbF was observed in thalassemia major cases and HbS was observed in sickle cell anemia.

On the basis of peripheral smear findings, following observations/results were made

1. Microcytic hypochromic picture along with target cells and nRBCs were observed in the smears of thalassemia major patients.

2. Sickle cells were observed in the smear of patient with sickle cell anemia.

3. Spherocytes and micro spherocytes were observed in the smears of hereditary spherocytosis.

Photographs

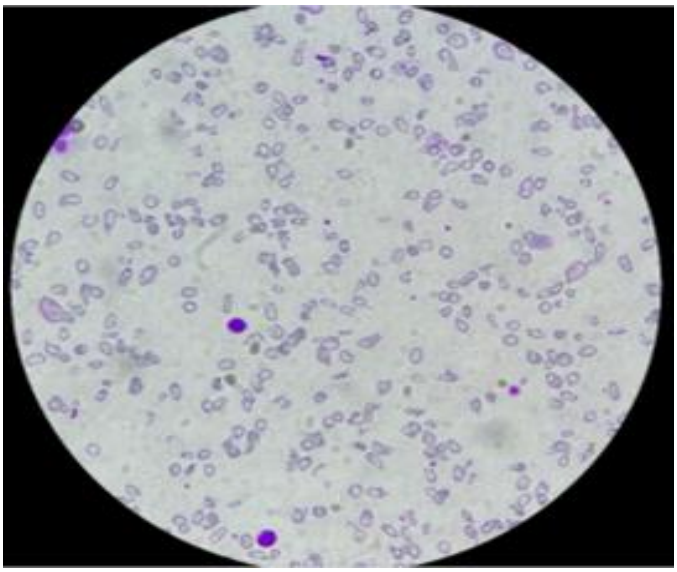


Figure 3: On 400 x Anisopokilocytosis of red cells which are microcytic, hypochromic with few target, elliptical and tear drop cells.

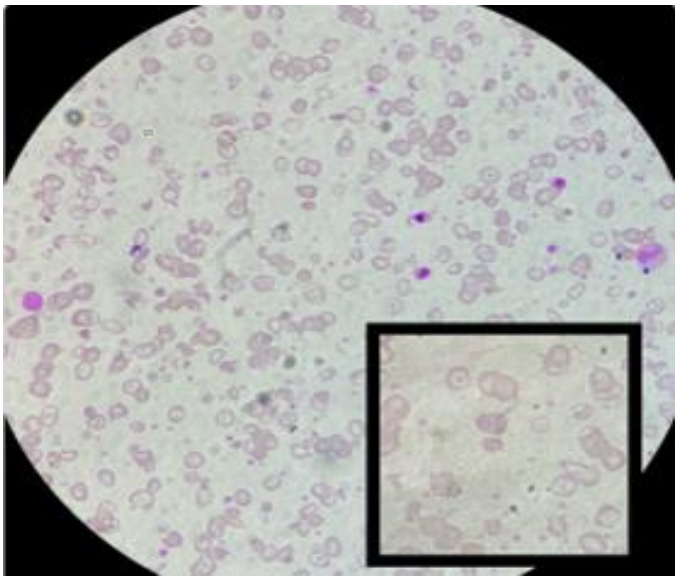


Figure 4: On 400x & 1000 x Microcytic hypochromic, target cells, nRBCs

Patients of thalassemia major showing hemolytic facies (Figure - 13,14,15,16,17)

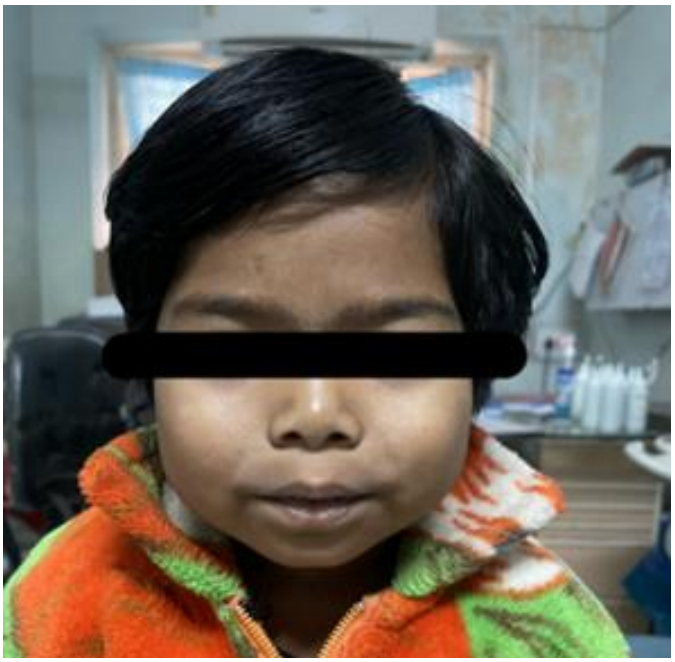


Figure 5:

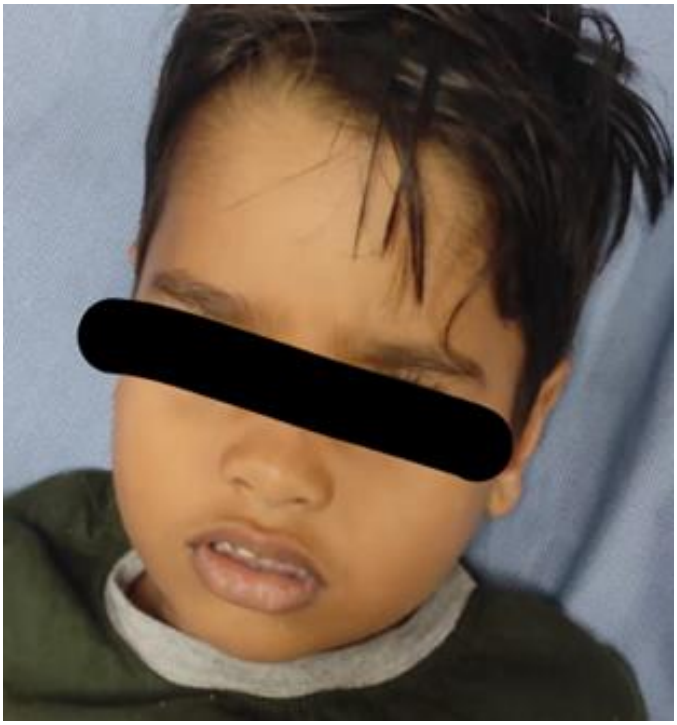


Figure 6:

Figure 7:

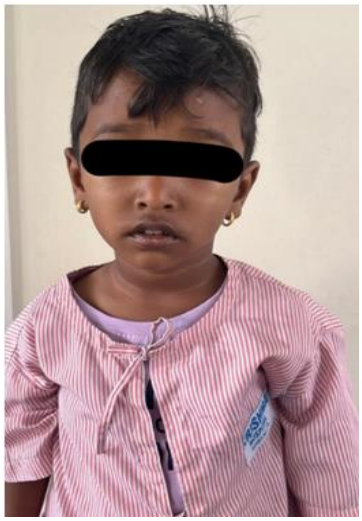


Figure 8, 9: Patients of thalassemia major showing hepatosplenomegaly (Figure - 18,19)

Figure 10:

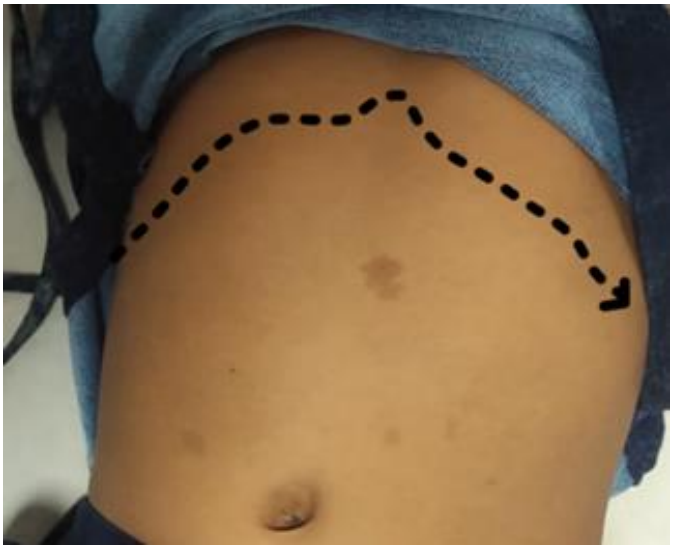


Figure 11: Patient of thalassemia major showing icterus with hemolytic facies

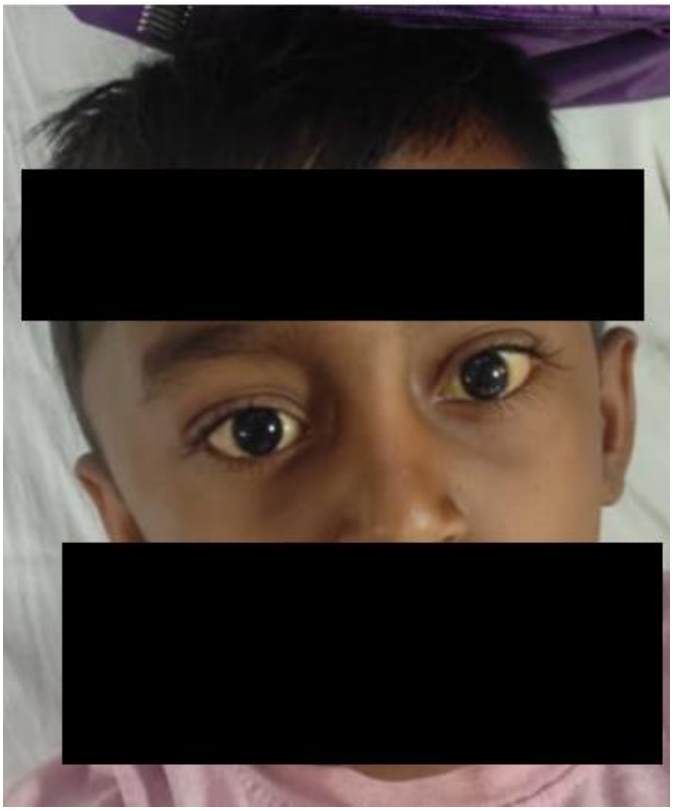


Figure 12: Patient of thalassemia major showing 'Hair on end' appearance on skull X-ray.

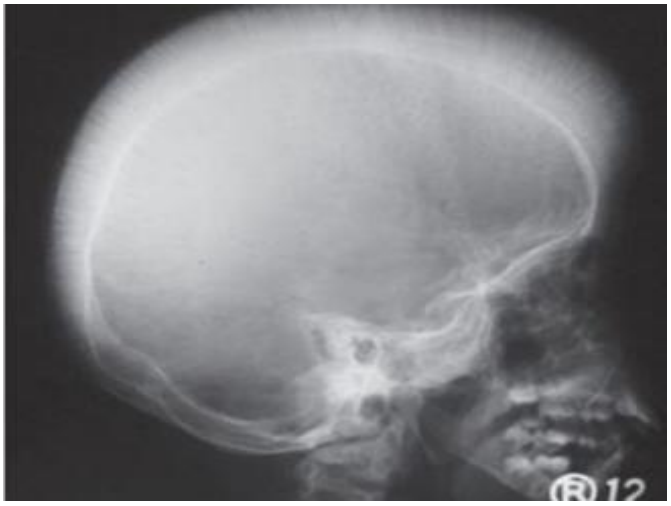


Figure 13:

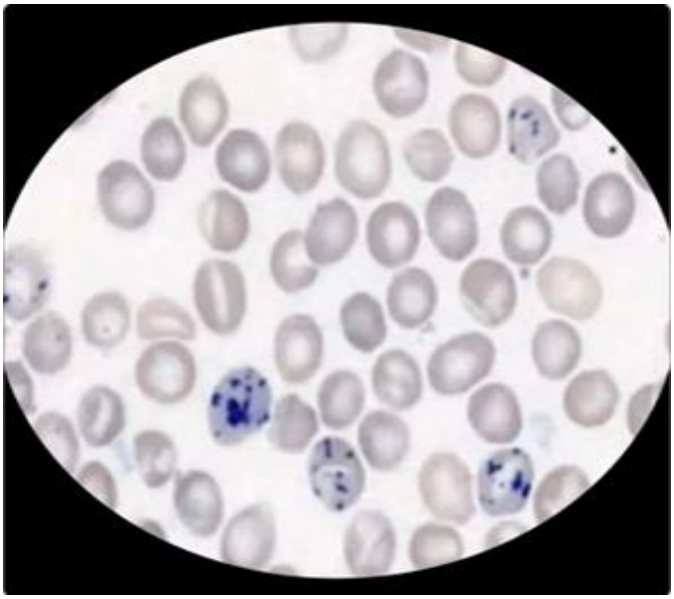


Figure 14: On 1000x – Reticulocytosis

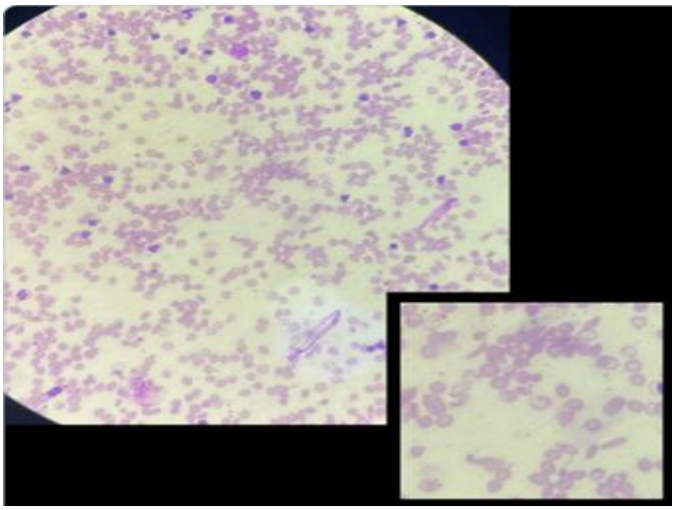


Figure 15: On 400x & 1000x – Sickle cells

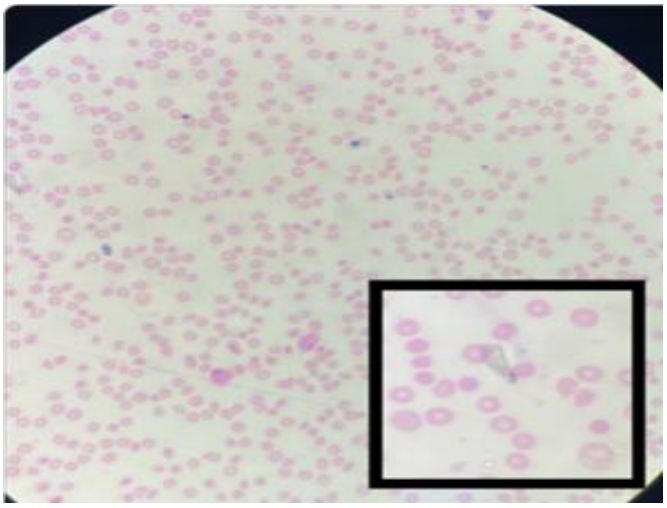


Figure 16: On 400x & 1000x – Spherocytes

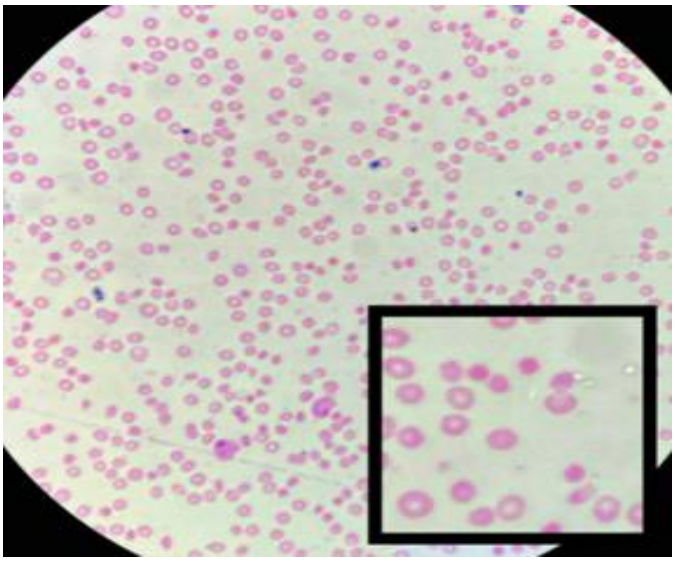


Figure 17: On 400x & 1000x – Micro spherocytes

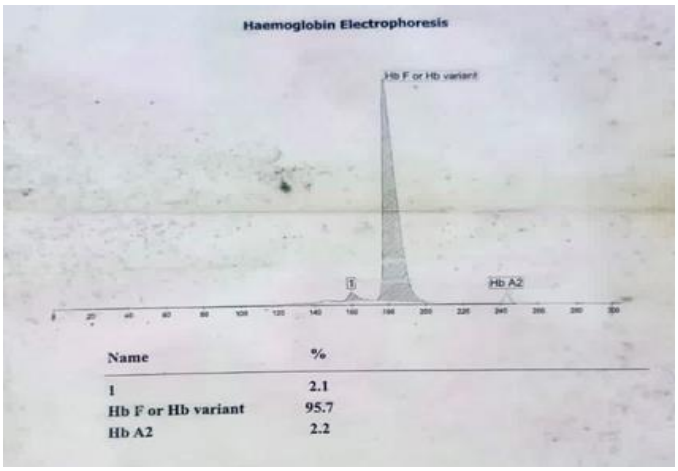


Figure 18: Hemoglobin electrophoresis of a thalassemia major patient showing HbF – 95.7

Discussion

40 cases were included in this cross-sectional clinic hematological correlation study of hemolytic anemia and the diagnosis was determined using the clinical and laboratory findings.

Incidence of hereditary hemolytic anemia is 0.1 - 0.2%.[5]

Beta thalassemia major was identified as the most prevalent hemolytic anemia.

Similar studies were carried out by — Deshpande et al[6], Shah Sajal et al[7], Virendra et al[8], Preethi et al[9], and Rahman et al[10] — contributed similar results.

Thalassemia syndromes have frequently been recorded from India's Western region[11] as opposed to sickle cell anemia, which is more frequently observed from the country's Eastern region.

According to a study by Ambekar et al[12] conducted in Pune, thalassemia syndromes are the most frequently prevalent. Our investigation also revealed more number of patients who are thalassemic.

In our study, 75.7% cases were in the age group ranged from 1 to 15 years, which is comparable to Kastubh Chattopadhyay et al[13] findings; that the youngest age group in their study was under 17 years old.

Similar findings are shown by Deshpande et al[6], Shah Sejal et al[7], Virendra et al[8], Preethi et al[9] and Anusha Raavi et al[14] with the most prevalent age range being 1-6 years.

In the present study, the hemoglobin varied from 2 to 9.4 g/dl in beta thalassemia major, with a mean of 6.56±1.90.

Similar results were observed in the study by Kastubh Chattopadhyay et al[13] which had mean Hb of 5.4±0.7, Virendra et al[8] had mean Hb of 6 g%, Preethi et al[9] varied from 3-11 g%, in Anusha Raavi et al[14] had mean Hb of 4.1±1.009 and in Deychen D Myes et al[19] had mean Hb of 5.2g% had mean Hb of 5.25 g%.

In our analysis, there were 5 cases of beta thalassemia trait (12.5%), with the majority of cases (60%) occurring in the reproductive age group.

Similar results were found by Chaitra et al[15] in which 28.2% i.e., most of their patients were in the reproductive age range at the time of carrier status diagnosis.

In our study, a screening test called the NESTROFT was used. According to the study of Praveen et al[16], this test was used as a screening test and our findings were similar to this study.

In this study, one patient showed hereditary sphero cytosis. Hypersplenism or crisis related characteristics were absent. In case with hereditary spherocytosis, the patient's hemoglobin was 12 g%, MCV was 80 fl, MCH was 29 pg., MCHC was 37 gm/dl, and the reticulocyte count was 5%, with spherocytes present in the peripheral blood smear.

Studies on hereditary spherocytosis that looked at hemo globin, MCV values, MCHC, and reticulocyte count by Delhomme au et al[17] found similar results.

In this study, one case of sickle cell anemia was diagnosed. Hemoglobin levels in the sickle cell anemia patient were 6 g%, MCV was 75.8 fl, MCH was 24.2 pg, MCHC was 32 gm/dl, and the patient had a 3% reticulocyte count with sickle cells, occasional target cells, and mild normoblastosis in the peripheral blood smear. Hepatomegaly was present in the patient.

All of the variables compared favorably to earlier studies of a similar nature conducted by Juwah et al.[18]

In the current study, there is a 67.5% male pre ponderance as compared to 32.5% female patients - Deshpande et al[6], Shah Sejal et al[7], Virendra et al[8],

Chaitra Venkata swamy et al[15], Preethi et al[9] and Deychen D. Myes et al[19]; all reported similar findings.

Out of 40 cases of hereditary hemolytic anemia in the current study,

23 cases (57.5%), show a history of consanguinity, which is further subdivided into the first, second, and third degrees.

In that, second degree consanguineous marriages were discovered to be the most prevalent amongst them, which is comparable to the study conducted by Preethi et al[9] who found 55% patients showing history of con sanguineous marriage with second degree con sanguinity most commonly observed.

- Similar results to those found in our study are also shown by Anusha Raavi et al[14] and Virendra et al[8]. In their study, they found 37% and 15% of patients showing history of con sanguineous marriage respectively.

In our study, 77.5% of cases had elevated urobilinogen.

Similar to the results of our investigation, David Roxe et al[20] also indicated that there is an increase in urobilin ogen in patients who undergo hemolysis.

Routine urine tests were also carried out, and the results revealed that 15% of patients had elevated hemosiderin Uria and 30% of patients had hemoglobinuria. According to W. Bar Cellini et al[21], these are the hemolytic indicators used in the differential diagnosis and treatment of hemolytic anemia.

In our study, all cases had total serum bilirubin levels >1mg/dl which is similar to the findings of the study done by Virendra et al.[8]

- The mean total serum bilirubin levels in beta thalassemia major was 3.81 mg/dl, 2.1 mg/dl in beta thalassemia trait and 2 mg/dl in hereditary spherocytosis which were found similar to the findings observed in the study of Anusha Raavi et al[14] which showed 3.1 mg/dl, 1.6 mg/dl and 1.8 mg/dl respectively.

- Also, Kastubh Chattopadhyay et al[13] reported the mean value of total serum bilirubin as 3.4 mg/dl in thalassemia major which were similar to the findings in our study.

Different types of hemolytic anemias were reported to have higher S. ferritin levels.

In our study,

- The serum ferritin level in beta thalassemia major was 1384.12±101.52.
- Serum ferritin was 1468 ng/ml in patient with sickle cell anemia.
- Similar results were found by Kastubh Chattopadhyay et al[13] who found that patients with beta thalassemia major had s. ferritin levels of 1718.7±1487.
- Similar results from Virendra et al[8] showed s. ferritin levels >1000ng/ml.
- Anusha Raavi et al[14] found that beta thalassemia major patients had s. ferritin levels of 1427.8, which is similar with the results of our investigation.

The clinical data revealed that anemia and pallor were the most prevalent findings since most patients had low hemoglobin levels.

- Jaundice, splenomegaly and hepatomegaly were also noted in most of the cases.
- Similar findings were observed in the studies of Kastubh Chattopadhyay et al[13], Shah Sejal et al[7], Chaitra Venkata Swamy et al[15], Preethi et al[9] and Anusha Raavi et al[14].
- Growth retardation (33.3%) and hemolytic facies (66.7%) were observed in beta thalassemia major patients.
- In the study done by Kastubh Chattopadhyay et al[13] who found that there was growth retardation in 23.6% and hemolytic facies in 53.2% of cases.

Conclusion

- In addition to anemia/pallor; which is the most frequent clinical finding in hemolytic anemia, other clinical symptoms included hepatosplenomegaly, weakness, failure to thrive, hemolytic facies, jaundice/icterus, and growth retardation.
- Hematological studies, peripheral smear examination and biochemistry studies assist to determine the type and degree of anemia.
- Microcytic hypochromic anemia could be seen in all thalassemia major cases.
- Majority of the cases were seen in males (67.5%).
- Elevated bilirubin was discovered, which is a strong biochemical indicator of hemolysis.

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