Profile of Anemia with special reference to hemoglobinopathies in a tertiary care centre in Madhya Pradesh

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Abstract

Introduction: Haemoglobinopathies constitute very important causative factors for anemia of childhood, especially in those regions where abnormal hemoglobin genes are highly prevalent. Thalassemia and Sickle cell anemia can be prevented by proper genetic counseling and screening. **Material Methods:** This cross-sectional one year study was conducted at Sri Aurobindo hospital Indore in department of pediatrics with the primary objective is to find out clinical and hematological characteristics of anemia with special reference to hemoglobinopathy. A total of 100 subjects were included. **Results:** The mean age of patients was 4.63 ± 4.18 years. Prevalence of Iron deficiency anemia was 61%, Vitamin B12 deficiency was 12%, thalassemia trait 10%, sickle cell anemia 10% and thalassemia major was 7%. , Mean Hb concentration was 6.54±1.63 g/dl and the MCV values ranged between 59.2±5.8 and 100.7±13.9. Mean reticulocyte was found 3.85±2.11 in thalassemia major, 4.0±2.10 and4.6±2.5 in sickle cell anemia. Mean HbA2 level was 2.45±0.69, in thalassemia major, 5.13±0.61 in thalassemia trait, and 2.01±0.71 in sickle homozygous. Mean HbF level was 92.57±1.6 in thalassemia major, 2.15±1.24 in thalassemia trait and 20.2± 9.6 in sickle cell anemia. **Conclusion:** HPLC is a reliable method for screening of thalassemia.Screening should be done among all suspected patients to find out the exact prevalence of thalassemia. Treatment should be started as soon as thalassemia positive is detected before the end organ damage has occurred. Genetic counseling of the patient's family for next pregnancy should be done to avoid birth of a thalassemia child in their family.

Key words: Anemia**,** Hemoglobinopathy, Thalassemia

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Introduction

Anemia is defined as a decreased concentration of hemoglobin as compared to the values in the age matched controls [1]. Anemic children have reduced exercise capacity, slower capacity of growth, impaired cognitive development, and delayed wound healing[2]. Anemia is an important indicator of nutritional status within the pediatric population [2]. As many as 20% children in the United States and 80% of the children in the developing countries are anemic at some point [3-5]. Most children with anemia are asymptomatic or have abnormal hemoglobin or hematocrit levels on routine screening. Infrequently a child with anemia may have pallor, fatigue and jaundice and may or may not be critically ill.

Thorough elicitation of history and findings on physical examination can reveal the underlying cause of anemia [1]. Symptoms of chronic anemia include irritability, pallor, icterus, glossitis, a systolic cardiac murmur, delayed growth and changes in the nail bed. Children with acute anemia often present more dramatically with clinical findings including jaundice, tachypnea, tachycardia, splenomegaly, hematuria and congestive heart failure [1].

Anemia in children may be due the presence of iron deficiency, glucose-6-phosphatase deficiency, pyruvate kinase deficiency, malnutritional, infection, and genetic. Most common genetic disorder in children is thalassemia and other hemoglobinoapthies. Laboratory diagnosis of anemia includes a complete blood cell count (CBC).Depending upon the Mean corpuscular volume (MCV) anemia can be classified into

microcytic, normocytic and macrocytic anemia[6-7]. Microcytic anemia may be due to iron deficiency and thalassemia and hemoglobinopathies.

Thalassemia and hemoglobinopatheis are hereditary anemia resulting from defects in hemoglobin production [8]. Thalassemia syndrome is an autosomal recessively inherited group of hemoglobin synthesis disorder characterized by the absence or reduction in output of one or more of the globin chains of hemoglobin. Depending upon the globin gene affected thalassemia is mainly of two types namely β thalassemia and α thalassemia [9].

β-Thalassemia, is caused by a decrease in the production of β-globin chains. It affects multiple organs and is associated with considerable morbidity and mortality [10]. It is a complex group of disorder because of the genetics of hemoglobin production and structure of hemoglobin molecule in which the normal hemoglobin protein is either not produced or produced in lower amounts than usual.

Hemoglobinopathy is a kind of genetic defect that results in abnormal structure of one of the globin chains of the Hb molecule [11]. The structural variants result from missense mutation that results in substitution of one or more amino acid in the globin chains of the hemoglobin. The best known hemoglobinopathy is sickle-cell disease, which was the first human disease whose mechanism was understood at the molecular level.

World Health Organization figures estimate that 5% of the world populations are carriers of a potentially pathological hemoglobin (Hb) gene [12]. Indian Council of Medical Research conducted a multicenter study in six states, and found that the overall incidence of beta thalassemia trait (BTT) was 2.78% [13]. Other studies from different parts of India have shown an incidence of beta thalassemia to be 3-15% [14-17]. The incidence of hemoglobinopathies also differs in different parts of India. In India, average frequency of Sickle cell gene is around 5%. The highest frequency of sickle cell gene in India is reported in Orissa(9%), followed by Assam (8.3%), Madhya Pradesh(7.4%), Uttar Pradesh(7.1%), Tamil Nadu(7.1%) and Gujarat(6.4%) [18-20].

Haemoglobinopathies constitute very important causative factor for anemias of childhood. This is especially so in those regions where abnormal hemoglobin genes are prevalent in a frequency of high order. Thalassemia and Sickle cell anemia can be prevented by proper genetic counseling and screening. With this background the study was undertaken to screen the anemic population of Indore for the thalassemia and hemoglobinopathies by HPLC (High performance liquid chromatography)/electrophoresis for hemoglobin variations and to offer counseling accordingly.

Material and Methods

This cross sectional, descriptive study was conducted on 100 patients in the age group of 6 months to 18 years, who were admitted to the pediatric ward of Sri Aurobindo Medical College and PG Institute, Indore with anemia from March 2013 to June 2014 to find out causes of anemia, the contribution of thalassemia and other hemoglobinopathies among these anemic children and to establish correlation of simple clinical and laboratory parameters like RBC indices with Hemoglobin abnormalities.

The children with hemoglobin values of less than 11gm/dl in the age group of 6 months to 6 years and those with hemoglobin values of less than 12 gm/dl in the age group of 6 to18 years were included in the study. Patients who do not give consent or had received blood transfusion within 1 month, had leukemia or any other malignancy or any chronic illness were excluded from the study.

The following operational criteria were used:

WHO criteria to define anemia as Hb% <11gm/dl among children between 6 months to 6years and Hb% <12gm/dl among children between 6 years to 14 years.

WHO criteria for grading of anemia as Mild–Hb% between10-12 gm%, Moderate–Hb% between 7– 10gm% and Severe–Hb% <7gm% [21].

The categorization of RBCs as microcytic, normocytic and macrocytic based on the MCV values was as follows:

Microcytic when MCV was <70 fl among children <1year, MCV was <73 fl among children between 1year to 5years and MCV was <75 fl among children >5years.

Normocytic when MCV was within the normal range

Macrocytic when MCV was >100 fl. Reduced Hb% and RDW >15% associated with microcytes was considered diagnostic of **IDA**, which was further confirmed by serum ferritin values of <12µgm/dl and reduced iron stores in bone marrow on staining with Perl's stain.

Megaloblastic anemia was diagnosed when peripheral smear showed macrocytic anemia with megaloblastic features, along with a MCV >100 fl, associated with leucopenia, thrombocytopenia and a reduced reticulocyte count. Diagnosis was done by demonstration of megaloblastic change in the bone marrow and reduced serum B12 level (<80pg/ml).

The diagnostic criteria for **hemolytic anemia** were peripheral smear with evidence of red cell breakdown in the forms of schistocyte, crenated RBCs, with associated normoblastosis, increased reticulocyte count and predominance of morphological variants like target cells in thalassemia and spherocyte in HS. Based on the morphology of RBCs, RDW and altered red cell indices, the specific investigations required were undertaken.

The cases which showed marked anisopoikilocytosis with features of microcytic hypochromic anemia, predominance of target cells and a reduced RDW were diagnosed to have thalassemia and were subjected to Hb electrophoresis/HPLC for confirmation of diagnosis. Assessment of Hb type was done using either electrophoresis or HPLC.

A detailed history was elicited, a thorough clinical examination was undertaken and the data was recorded using a proforma. The required quantity of venous blood was collected in EDTA tubes. The collected blood was analyzed using coulter LH 750 analyzer (figure), having three part differentials, from which the following parameters were obtained: Hb%, PCV, RBC count, RBC indices including MCV,MCH,MCHC, Platelet count and Total WBC count.

Peripheral smears were prepared on glass slides and stained with Leishman's stain. The reticulocyte count was done by the supravital staining technique using Brilliant cresyl blue. Among the microcytic hypochromic anemia cases, iron deficiency anemia was diagnosed by serum ferritin estimation. The hemolytic anemia cases which were suspected on clinical and peripheral blood examination were taken up for a complete hematological workup including Hb electrophoresis, osmotic fragility depending on the specific requirement.

High Performance Liquid Chromatography: We used ClinReP HPLC Complete Kit for the determination of haemoglobin variants and for the screening of β-thalassemia in whole blood. The samples were prepared within a short sample preparation and were injected into the HPLC system subsequently. At this, the sample components were chromatographically separated and the analyteswere detected by the UV/VIS detector.

Whole blood was used for sample preparation.The blood samples were hemolysed with hemolysis reagent and incubated for 10 min at ambient temperature subsequently. Afterwards an aliquot of the prepared sample is injected into the HPLC system.

The calculation of the measurements was performed by using the area-percent-method. The amount of the particular Hemoglobin (HbF, HbA, Hb A2) is expressed as percentage of the sum of the total hemoglobin peak area. In case of HbF and HbA2, the determined values are multiplied with the corresponding calibration factors. The calibration factors are calculated separately for both hemoglobin's and for every series of analysis.

Statistical Analysis: Statistical analysis was done using SPSS software version 15. Quantitative variables were analyzed by student t test whereas Chi Square test was used to estimate difference in frequencies of discrete variables.

Results

Out of 100 subjects 47 were females and 53 males. Male to female ratio was 1.3:1. The mean age of patients was 4.63 ± 4.18 years (range 6 months to 15 years). Most common age group affected was toddler (1-3 years) constituting 37%, followed by > 5years constituting 27% followed by infant (6 months to 1 years) constituting 19 % with least in preschool (3 years to 5 years) constituting 17 %. Among hemoglobinopathy age group most commonly affected was more than 5 year (46%) and least affected was age group 6 months to one year (6%).

Table 1: Age and sex distribution in different anemic groups

Parameter	Male	Female	Total	Mean Age(years)
B12 Deficiency	5	7	12	5.41±5.2
IDA	32	29	61	3.59±3.41
SCA	6	4	10	6.14±4.35
TM	3	4	7	2.70±2.44
TT	7	3	10	10.0±3.6
Total	53	47	100	4.63 ± 4.18

Iron Deficiency anemia was observed in the majority (61%) of cases and the mean age of presentation in IDA was 3.59 ± 3.41 years (10 months -15 years). IDA was more common in males than females. The prevalence of Vitamin B12 deficiency was 12 % and sickle cell disease was 10 % respectively. Ten patients were found as carrier for thalassemia gene while seven had thalassemia major. (Table 1)

Mean Hb concentration in studied patients was 6.54±1.63 g/dl. The mean Hb level in thalassemia major patients was 6.28±1.75 gm/dl. In Sickle cell anemia patients the mean Hb level was 6.5±1.7gm/dl. The mean Hb levels were almost similar in all the types of anemia (p value 0.471). (Figure 1)
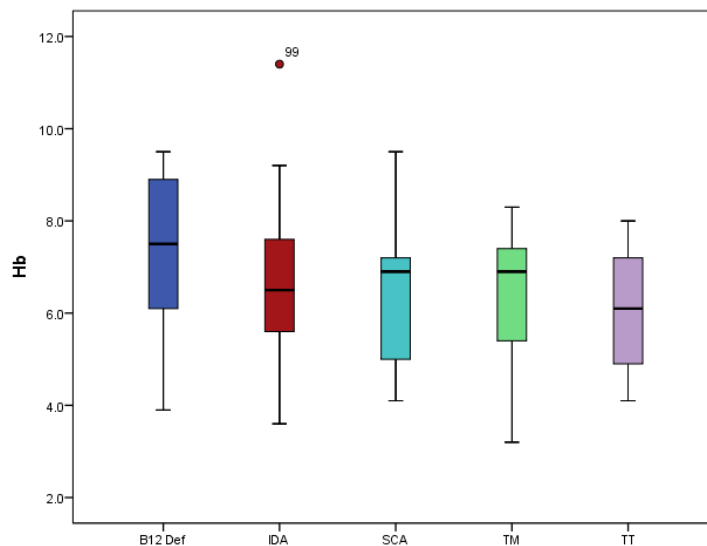

Figure-1: Hb levels in different type of anemic patients

Mean corpuscular volume was decreased (<76 fl) in all types of anemia except in patients with vitamin B12 deficiency cases. Table 2 shows the average MCV values in all types of anemic patients. We observed that iron deficiency patient had lowest MCV values (59.15±5.8 fl). MCV values were almost similar in thalassemia major, thalassemia trait and sickle cell anemia patients.

Table 2: MCV and MCH in different types of anemia

Diagnosis	MCV	MCH
B12 Deficiency	100.7±13.9	26.3±3.8
IDA	59.2±5.8	19.3±2.6
SCA	63.3±10.6	21.5±3.1
TM	69.5±5.2	20.3±4.4
TT	64.4±8.2	19.7±3.8
Hemoglobinopathy (SCA+TM+TT)	65.3±8.6	20.5±3.6

Mean corpuscular hemoglobin was also decreased in all type of anemia except Vitamin B12 deficiency patients. It was least in iron deficiency anemia cases. Of the hemoglobinopathies patient the MCH values were lowest in thalassemia trait patients (table 2).

When we compared MCV and MCH values in hemoglobinopathies and Iron Deficiency anemia group, significant difference was found in MCV values only (P value <0.0001). MCH values were almost similar in IDA and hemoglobinpathy group (p =0.079). However there was no significant difference in MCV and MCH values of thalassemia major, thalassemia trait and Sickle cell anemia patients. Therefore on the basis of MCV and MCH values alone we cannot differentiate between the types of hemoglobinopathy.

Reticulocyte count was also found normal in vitamin B12 deficiency cases (0.95±0.64%) and it was near normal in iron deficiency anemia patients (2.0±0.86%). (Table 3)

Table 3: Reticulocyte count in different anemic patients

Diagnosis	Reticulocyte Count
B12 Deficiency	0.95±0.64
IDA	2.0±0.86
SCA	4.6±2.5
TM	3.85±2.11
TT	4.0±2.10
Hemoglobinopathy (SCA+TM+TT)	4.18±2.23

Highest reticulocyte count was observed in sickle cell anemia patients showing highest degree of hemolysis on sickle patients (Table 3). Reticulocyte count was significantly higher in hemoglobinopathies group than iron deficiency and Vitamin B12 deficiency group (p<00001).

Serum Iron and Total iron binding capacity was measured in all the microcytic hypochromic anemic patients to differentiate the Iron deficiency and hemoglobinopathies or any other cause. The percent transferrin saturation was calculated as Serum Iron/TIBC *100. If percent transferrin saturation was less than 16 then patient was classified as Iron deficiency anemia. The mean % transferrin saturation in IDA patients in our study was 4.9±3.1% whereas in hemoglobinopathy group it was 51.9±123.8%. (Table 4)

Table 4: Iron Profile in all patients

Diagnosis	SI	TIBC	% Transferrin
B12 Deficiency	57.8±15.5	247.1±42.2	23.17±2.6
IDA	22.98±10.1	508.40±92.4	4.9±3.1
SCA	36.80±20.2	340.80±153.3	21.5±10.6
TM	98.8±512.8	398.2±168.9	25.1±8.6
TT	108.4±109.7	250.8±143.8	116.1±213.8
Hemoglobinopathy (SCA+TM+TT)	81.3±73.7	329.9±157.0	51.9±123.8

HPLC/electrophoresis was performed in all the microcytic anemia cases without iron deficiency to differentiate the sickle cell anemia, thalassemia trait and thalassemia major.

Out of 27 microcytic hypochromic patients with normal iron levels sickle cell anemia was found in 10 cases. 10 patients were thalassemia trait and 7 were thalassemia major. Accordingly sickle cell anemia patients were further classified into sickle cell homozygous anemia, sickle cell trait and sickle beta thalassemia. (Table 5)

Table 5: HPLC pattern in different hemoglobinopathy group

Diagnosis	HbA	HbA2	HbF	HBS
TM(7)	3.6±1.5	2.45±0.69	92.57±1.6	-
TT(10)	92.37±1.61	5.13±0.61	2.15±1.24	-
Sickle homozygous(4)	9.8±9.7	2.01±0.71	20.2±9.6	72.31±15.2
Sickle beta thalassemia(4)	18.7±2.4	4.75±0.35	16.0±0.0	60.75±1.76
Sickle cell trait(2)	33.4±1.9	2.6±0.56	3.0±1.41	60.75±1.76

Discussion

One of the major areas for improvement in primary care is prevention of nutritional deficiency like anemia, because it has been associated with visual and auditory dysfunctioning, cognitive, behavioral abnormalities, and delay in psychomotor development [22]. Appropriate screening and subsequent diagnostic testing will allow most cases of anemia to be diagnosed at the earliest. This should be implemented by the primary care physicians to choose screen and treat approach to prevent complications of anemia at the level of primary care itself.

The inherited disorders of hemoglobin, particularly the β- thalassemia and their interaction with hemoglobin S (HbS) are a considerable health problem in India and contribute significantly to morbidity and mortality. Earlier studies have shown that the overall prevalence of β-thalassemia is 3–4 % with an estimate of around 8,000 to 10,000 new births with major disease each year [23,24].

Most of these children have a severe clinical presentation but are managed sub-optimally due to lack of financial resources in majority of the families. Thus preventing the birth of affected children is the best option. A prerequisite for this is the knowledge of the prevalence of β-thalassemia and other hemoglobinopathies in different regions of the country and in particular in different ethnic groups.

In the present study 57% of males were anemic and 43% of females were anemic with male to female ratio of 1.3:1. Most common age group affected were toddler age group (1-3 years) constituting 37%, followed by > 5years age group constituting 27% followed by infant age (6 months to 1 years) constituting 19% with least in preschool age group(3 years to 5 years) constituting 17 %.Among hemoglobinopathy age group most commonly affected was more than 5 years (46%) and least affected was age group 6 months to one year (6%).

In a similar study conducted at a multispecialty hospital of Bangalore [22], 58% males and 42% females were anemic with male to female ratio of 1.4:1.Most common age group affected were infants (6 month -1 year) constituting 33%., followed by school-going children (6 years-12 years, 26%), toddlers (2 years-3 years, 25%), and preschool children (4 years-5 years, 16%).Of the nonhemoglobinopathies, 33% children in the age group 6 months-1 year were most affected and 16% in the age group 4-5 years were least affected. Among hemoglobinopathies, 54% children in the age group 6-12 years were most affected, followed by 30% children in the age group 2-3 years and 8% in both the age groups 6 months-1 year and 4-5 years were affected.

According to the NFHS 2005-06 [25], 79% of the children in the age group of 6-35 months were anemic. In the study conducted by Gomber *et al.*, 76% of children were anemic in the age group of 3 months-3 years [26]. Osσrio *et al.*, reported the incidence of anemia to be 40.9% in the age group of 6-59 months [27].

Severity: In this study majority of children suffered from severe anemia and microcytic hypochromic anemia was the most common type with the highest proportion (33%) in 1 to 3 years age groups. Macrocytic anemia was the least common morphological type of anemia in all age groups (12%).

In comparison, study conducted at the multispecialty hospital of Bangalore depicted that most children in all the age groups suffered from moderate anemia and microcytic hypochromic anemia being the commonest with the highest number (29.39%) found among children of age group 6 months to 1 year and least number (11.92%) in the 4-5 years age group. Macrocytic anemia was the least common morphological type of anemia in all the age groups (10%).

While in the study conducted by Gomber *et al* [28] among children aged 5-5.9 years, mild anemia was found in 28.9% and moderate anemia in 2.9% of children. In another study conducted by Vishwanath *et al* [29] 89 of 100 children investigated had iron deficiency anemia and 48% had mild, 42% had moderate and 10% had severe anemia respectively.

Morphological types of anemia: In this study, microcytic hypochromic was the most common (76%) followed by normocytic normochromic (20%) picture followed by macrocytic anemia (4%) which are similar to the findings of the bangalore study where MCHA (49%) was most common followed by NNA (22%), and macrocytic (4%).

Our findings are also comparable to the study of Kapoor *et al* [30], in which MCHA was most common (43.2%) followed by equal incidence of NNA and dimorphic anemia (27%), while the least common was macrocytic anemia (2.7%). Gomber *et al* [31] found iron deficiency anemia to be the most common (41%) and folate deficiency to be least common (2.2%). This is different to our study findings as we excluded dimorphic anemia.

Red cell indices studied: In the present study, Mean Hb concentration was 6.54±1.63 g/dl and the MCV values ranged between 59.2±5.8 and 100.7±13.9 among the patients studied.

Our findings are comparable to the Bangalore study where mean Hb, and MCV was 8.5 g/dL and 75.08 fl respectively and study conducted by Herbert et al which had a mean Hb and MCV of 9.78 g/dL and 64.34 fl respectively [22, 31]. In the study conducted by Osorio, mean hemoglobin was found to be 11 g/dL [28].

Hemoglobinopathies: Patients with hemoglobinopathy syndrome are commonly encountered in a hematology clinic. Of these, the commonest disorder of hemoglobinopathy syndrome in India is thalassemia. Of the 27 children with haemoglobinopathies, 16 were males and 11 were females. Thus the male to female ratio was found to be 1.4:1. This is similar to the Bangalore study [22] where out of 13 children with hemoglobinopathies, 8 were males and 5 were females. Thus, the male to female ratio was found to be 1.6:1.

In our study out of 27 children of hemoglobinopathies ,majority were in the age group of >5 years (40.7%) followed by 3 to 5 years age group (33.3%) and the

least in infants age group. In another study by Saba et al [22] out of the 13 children with hemoglobinopathies, majority were in the age group of 6-12 years (53%) followed by 2-3 years (31%). There was an equal occurrence among 6 months-1 year (8%) and 4-5 years (8%).

Distribution of types of hemoglobinopathies: In the present study sickle cell anemia and thalassemia trait haemoglobinopathies had equal incidence seen in 37% each children followed by thalassemia major seen in 25.9% children. Our findings are comparable to the Bangalore study [22], where thalassemia major was the most common type of hemoglobinopathy seen in 54% children followed by thalassemia minor among 30% children and equal incidence of about 8% child each suffering from sickle cell anemia, and sickle cell thalassemia.

In the present study, homozygous thalassemia was the most common which is similar to the study conducted by Mitra [32], HbE was found to be the most common, followed by homozygous thalassemia and least common was HbDE disease.

Conclusion

HPLC is a reliable method for screening of thalassemia. Screening should be done to all suspected patient to find out the exact prevalence of thalassemia. Treatment should be start as soon as thalassemia positive detected before the end organ damage.Genetic council the patient family for next pregnancy for avoid birth of a thalassemia child in their family.

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