

Frequency and Clinico-Hematological Features of Pure Red Cell Aplasia in Children

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ABSTRACT

Objective: To study the frequency and clinical & hematological pattern of pure red cell aplasia in children.

Study Design: Prospective Descriptive study.

Place and Duration of Study: It was carried out in the department of Hematology and Transfusion medicine of the Children's Hospital and the Institute of Child Health, Lahore from June 2004 to December 2008.

Patients and Methods: This study included children up to 5 years of age who presented with pallor. Detailed history and examination was entered on a pre-designed performa, and relevant investigations were done. Children with normochromic normocytic anemia, low reticulocyte count and absent erythroid activity in the marrow were labeled as pure red cell aplasia. Other types of anemia were diagnosed according to their respective diagnostic criteria. Data was analyzed using SPSS version 10 on computer.

Results: Out of 1800 children of anemia, deficiency anemia was diagnosed in 1640 children (91.1%), hemolytic anemia in 120 children (6.67%), pure red cell aplasia in 30 children (1.6%), congenital dyserythropoietic anemia in 08 children (0.4%) and sideroblastic anemia in 2 children (0.1%). Out of 30 children of pure red cell aplasia, Diamond Blackfan anemia was diagnosed in 23 children (80%) and transient erythroblastopenia of childhood in 7 children (20%). The mean age of DBA (Diamond Blackfan Anemia) was 4.12 ± 3.21 months and male:female 1:1.5, while in TEC (Transient Erythroblastopenia of Childhood) it was 3.80 ± 2.01 years, and the male:female was 1:1.3. Fever and history of preceding viral infection was present in 100% cases of TEC, while in DBA fever was present in 60% cases without history of preceding viral infection. Reticulocyte count in DBA and TEC was <0.5% and <0.3% respectively. Absent and reduced erythropoiesis in bone marrow examination was found in both the entities.

Conclusion: Pure red cell aplasia constituted about 1.6% of all anemia in children less than 5 years of age.

Key Words: Pure red cell aplasia, Diamond Blackfan Anemia, Transient Erythroblastopenia of childhood

INTRODUCTION

Pure red cell aplasia is a syndrome characterized by normochromic, normocytic anemia, reticulocytopenia (<1%), and an almost complete absence of erythroblasts (<0.5%) from the bone marrow¹.

In pediatric age group, pure red cell aplasia is categorized as:

1. Congenital: Diamond Blackfan Syndrome or Congenital Hypoplastic Anemia
2. Acquired: a) Transient Erythroblastopenia of Childhood (TEC) b) Parvovirus induced aplastic crises².

In Diamond Blackfan syndrome, infants present

at 2-3 months of age with symptoms of anemia. The exact pathogenesis of Diamond Blackfan syndrome is not known. The basic abnormality seems to be an intrinsic defect in the erythroid cells that prevents their differentiation into mature erythroblasts. Anemia is evident at birth in 25% of cases. Associated physical abnormalities are present in 50% children, which include craniofacial abnormalities, thumb anomalies and growth retardation. The minimal diagnostic criteria for Diamond Blackfan anemia generally include normocytic, normochromic anemia in infancy (less than 2 years), low reticulocyte counts and absent or decreased bone-marrow dead cell precursors (less than 5% of nucleated cells). Additional features include presence of malformation, macrocytosis, elevated fetal hemoglobin and elevated erythrocyte adenosine deaminase (eADA) level. The bone-marrow aspirate is usually

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normocellular but erythroblasts are markedly decreased or absent³.

Transient erythroblastopenia of childhood is an acquired, self limiting red cell aplasia that is unique to childhood, characterized by the temporary arrest of red cell production resulting in moderate to severe anemia⁴. Results from repeated studies indicate that the arrest of erythropoiesis is caused by presence in the patient's plasma of an erythropoietic inhibitor. This inhibitor has been localized to immunoglobulin G (IgG) fraction and it disappears from the plasma after remission of pure red cell aplasia⁵. The commonest age at presentation is 2 years. Thus transient erythroblastopenia of childhood tends to presents in an older age group than Diamond Blackfan anemia. Boys and girls are equally effected, there are no associated physical anomalies and effected children are generally of normal stature. Many children give the history of antecedent viral infection.⁽³⁾ Diagnosis of transient erythroblastopenia can only be made after exclusion of known causes such as drugs, viruses, immune deficiency, leukemia and of Diamond blackfan disease⁶.

Parvovirus B-19 a member of erythrovirus genus is pathogenic. This DNA virus has been known to cause erythema infectiosum or fifth disease in children. Hematological consequences of B-19 infection arise due to a direct cytotoxic effect on erythroid progenitor in the bone marrow with interruption of erythrocyte production⁷.

PRCA is one of the important causes of childhood anemia. Therefore, the rationale of this study is to calculate the frequency of pure red cell aplasia out of all the cases of anemia in children under 5 years of age and also to study its clinico-hematological features.

MATERIALS AND METHODS

It was a hospital based descriptive study which was conducted in the department of Hematology and Transfusion Medicine of the Children's Hospital and the Institute of Child Health, Lahore. This study was carried out from September 2004 – December 2008. Total number of patients who were diagnosed as a case of anemia was 1800. The sampling procedure was purposive type of non-probability sampling.

Children included in the PRCA category were 0-5 years of age presenting with pallor, having normochromic normocytic or macrocytic anemia with low RBC count and low reticulocyte count with very low or absent erythroid activity in the bone marrow. Those having Pancytopenia on complete blood count or a Lymphoproliferative disorder or drug induced red cell aplasia were excluded.

A performa was designed containing the detailed history, complete physical examination and relevant investigations (based on history). Every case of anemia was given a case number. Name of the child, age, sex, father's name and address were documented on the performa.

Detailed clinical history regarding the onset and duration of pallor symptoms (such as poor feeding, lethargy, weight loss, breathlessness), history of preceding viral illness, history of blood transfusion and any family history of pallor was documented. Then complete physical examination was carried out with special importance given to height, weight, signs of pallor, jaundice, presence of physical anomalies (cleft or high arched palate, thumb anomalies, flat nasal bridge and hypertelorism), hepatomegaly and splenomegaly. All positive points of clinical significance were recorded on the performa.

Based on the history and physical examination, following investigations were done in all children i.e. complete blood count (on hematology analyzer), peripheral smear examination, and reticulocyte count, while bone marrow examination was done where indicated. Regarding data analysis as the study was descriptive it did not require any correlation. In case of quantitative data such as age, a t test was applied. Range, mean, standard deviations and percentages are given for red blood cell count, hemoglobin, white blood cell count, platelets and reticulocyte count.

RESULTS

The data of various parameters obtained was analyzed and presented in the form of figures and tables. Total number of anemic patients, presented during the study period was 1800. Out of these 1800, the number of children with deficiency anemia was 1640, the number of children with various hemolytic anemias (thalassemia, autoimmune hemolytic anemia, sickle cell anemia, etc) was 120, the number of children with pure red cell aplasia was 30, while 08 children presented with congenital dyserythropoietic anemia and 02 with sideroblastic anemia (Figure.1). This figure shows that pure red cell aplasia in children constituted about 1.66% of total anemic patients.

Out of the total 30 cases of pure red cell aplasia, 23 (76.7%) children were diagnosed to have Diamond Blackfan anemia and 07 (23.3%) children were diagnosed as transient erythroblastopenia of childhood (Figure 2), with a 'p' value of < 0.001 that was statistically highly significant.

Out of thirty cases of pure red cell aplasia, 18 (60%) were females and 12 (40%) males making a male: female ratio of 1:1.5. In Diamond Blackfan anemia (n=23), male: female was found to be 1:1.5

as there were 09 males and 14 females, while in transient erythroblastopenia of childhood, male: female was found to be 1:1.3 (Figure 3). In Diamond Blackfan anemia, mean \pm SD age was found to be 4.12 ± 3.21 (months) while in transient erythroblastopenia of childhood, the mean \pm SD age was 3.80 ± 2.01 (years).

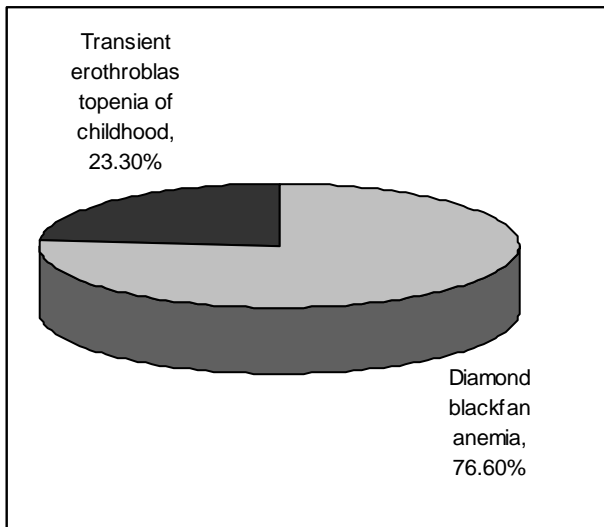
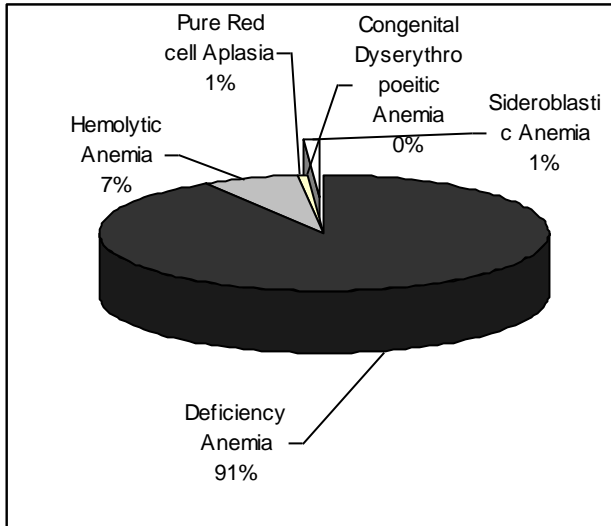


Fig. 2: Percentage of cases of Diamond blackfan anemia and Transient erythroblastopenia of childhood out of the total red cell aplasia (n=3)

The percentage of common presenting complaints in both Diamond Blackfan anemia and transient erythroblastopenia of childhood has been described as a bar chart in figure 4, while the findings of physical examination in Diamond Blackfan anemia are described as a bar chart in figure 5.

In transient erythroblastopenia of childhood, pallor was present in all cases, there was no jaundice, lymphadenopathy or splenomegaly and hepatomegaly of about 1cm below costal margin was seen in only one case.

Hematological Parameters including complete blood count & reticulocyte count of Diamond Blackfan anemia and Transient erythroblastopenia of childhood are described in Table 1 and Table 2 respectively.

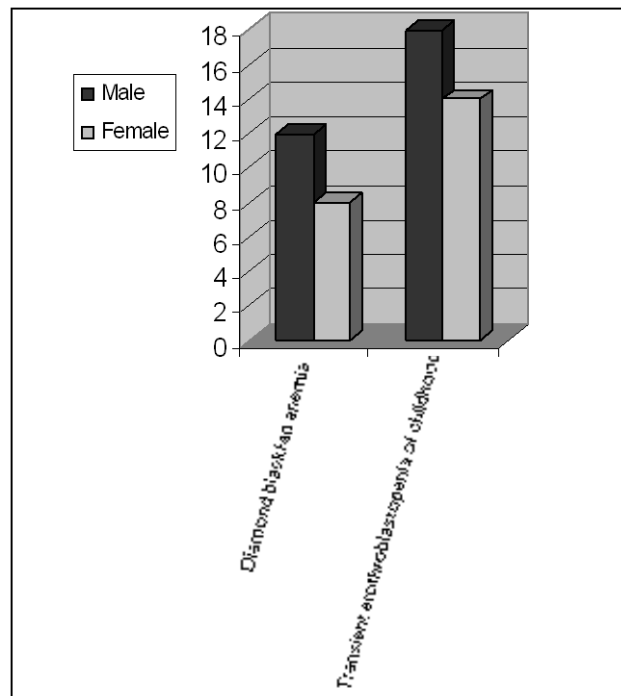


Fig.3: Distribution of sex in Diamond Blackfan anemia and transient Erythroblastopenia of childhood

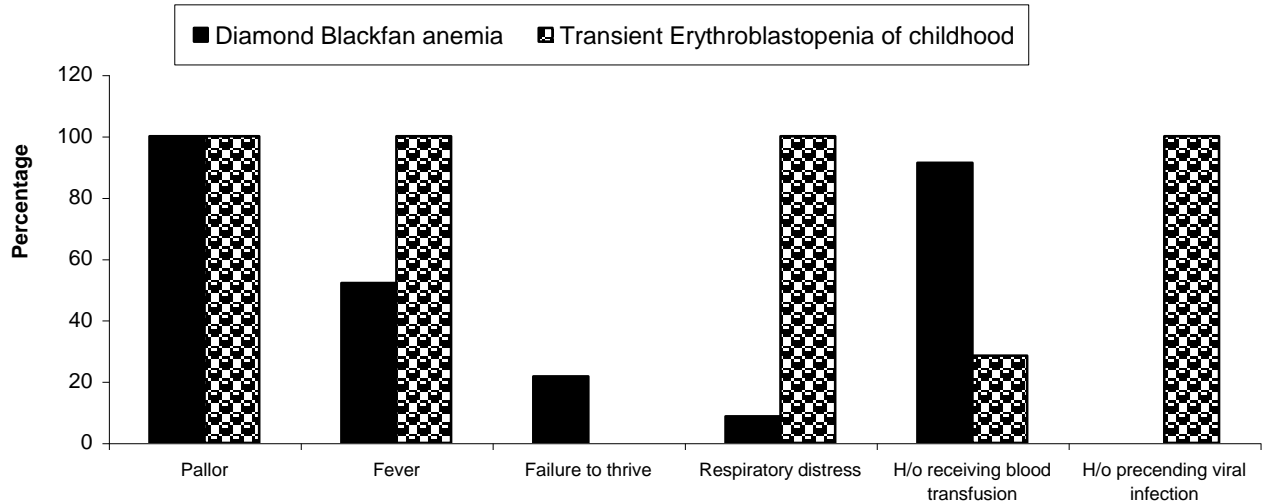


Fig.4: Common presenting complaints in Diamond Blackfan anemia and Transient Erythroblastopenia of childhood. FIF> %:

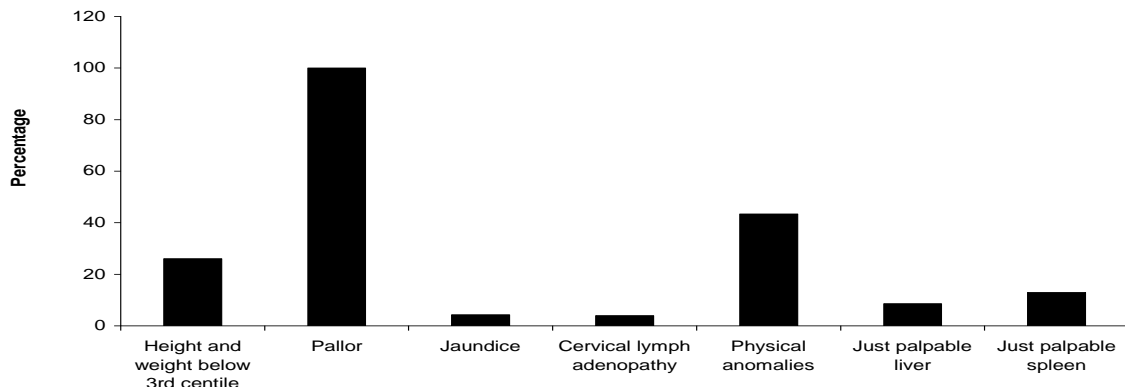


Figure 5: Physical examination in Diamond Blackfan anemia

Table1: Diamond Blackfan anemia

Complete Blood Picture	Range	Mean±SD
Red blood cell count	0.67x10 ¹² /L– 3.5x10 ¹² /L	1.88x10 ¹² ±0.9 /L
Hemoglobin Concentration	1.5g/dl – 9g/dl	4.97±2.31 g/dl
Total leukocyte count	3.26x10 ⁹ /L – 15.9x10 ⁹ /L	8.29x10 ⁹ ±3.39 /L
Platelet count	135x10 ⁹ /L – 538x10 ⁹ /L	280.7 x10 ⁹ ±153.66 /L
Reticulocyte Count	0.02 – 0.5	0.278±0.144

Table 2: Transient erythroblastopenia of childhood

Complete Blood Count	Range	Mean±SD
Red blood cell count	0.74x10 ¹² /L - 3.7 x10 ¹² /L	2.01x10 ¹² ±0.91 /L
Hemoglobin concentration	2.4g/dl – 10.4g/dl	5.44±2.51 g/dl
Total leukocyte count	4.2x10 ⁹ /L – 12.63x10 ⁹ /L	6.94x10 ⁹ ±2.8 /L
Platelet count	31x10 ⁹ /L – 268x10 ⁹ /L	211.14x10 ⁹ ±45.64 /L
Reticulocyte Count	0.02 – 0.3	0.21±0.13

Regarding RBC morphology, in Diamond Blackfan anemia, 19 cases had normocytic normochromic picture while 4 cases having macrocytic normochromic picture. In transient erythroblastopenia of childhood, 5 cases had normocytic normochromic picture while 2 cases having macrocytic normochromic picture. The percentage of normocytic normochromic and macrocytic normochromic in both Diamond Blackfan anemia and transient erythroblastopenia of childhood was found to be the same and are shown as a bar chart in figure 6.

Bone marrow examination of all the cases of pure red cell aplasia (Diamond Blackfan anemia and transient erythroblastopenia of childhood) showed either absent or markedly reduced erythropoiesis. The leucopoiesis and megakaryopoiesis were found to be normal.

Diagnosis of transient erythroblastopenia of childhood was made after exclusion of known causes such as drugs, immune deficiency, leukemia and Diamond Blackfan anemia.

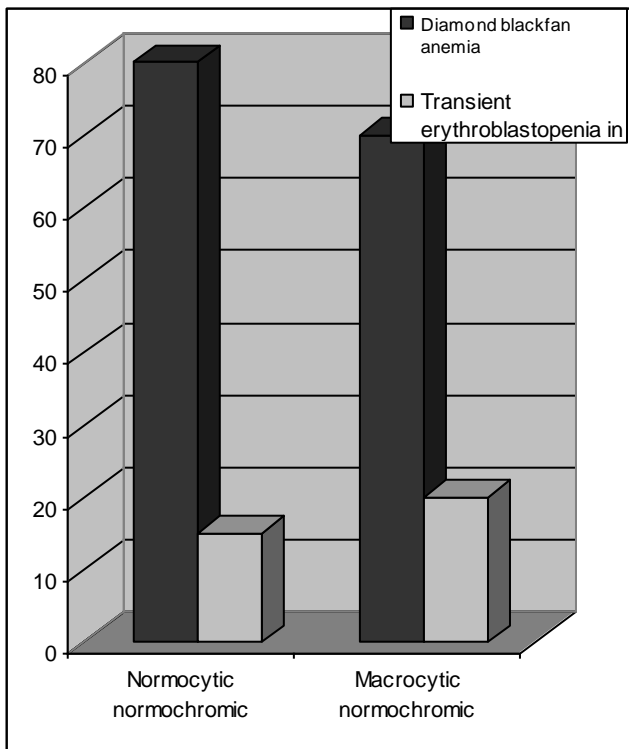


Fig. 6: Red blood cells morphology in Diamond Blackfan anemia and Transient Erythroblastopenia of childhood.

DISCUSSION

This study shows that deficiency anemia were more common as compared to other anemia. The study conducted by Paracha et al⁷ demonstrated that iron

deficiency anemia is a serious problem among Pakistani children and is the predominant cause of anemia in children under 2 years of age.

In our study pure red cell aplasia was found to be a rare disease constituting about 1.6% of total childhood anemia. Campagnoli et al⁸ described Diamond Blackfan anemia as a rare PRCA of childhood that is caused by an intrinsic defect in erythropoietic progenitors.

Diamond Blackfan anemia was diagnosed in 23 children (76%) and transient erythroblastopenia of childhood in 07 children (23%) out of the total of 30 children of pure red cell aplasia. A study regarding the clinico hematological profile of 16 patients of pure red cell aplasia was conducted by Marwaha et al⁹ in India, which showed that out of 16 patients of pure red cell aplasia, 14 had Diamond Blackfan anemia (87.5%), 1 had transient erythroblastopenia of childhood (6.25%) and 1 had pure red cell aplasia secondary to carbamazepine therapy (6.25%). Similarly Ikram et al¹⁰ in Pakistan showed an etiological break up of 14 cases of pure red cell aplasia where congenital pure red cell aplasia constituted the commonest etiological group (28.6%), followed by pure red cell aplasia associated with infections in 21.4%, with co-trimoxazole 14.3% and with systemic lupus erythematosus and rheumatoid arthritis (7.1% each) respectively. In 21.4% cases, no definite cause could be established. It seemed from these studies that the Diamond Blackfan anemia is more common as compared to transient erythroblastopenia of childhood in children which are diagnosed to have pure red cell aplasia.

The present study showed that the children with Diamond Blackfan anemia presented mostly in the 3rd month of life (47.8%) followed by the children who were diagnosed (in order of decreasing percentage) in the 2nd month (17.3%), in 1 month, 6 months, 4 months and 1 year of age (8.6% each). It means that most of the children were diagnosed by 3rd month of age. These findings are comparable to a study conducted by Ball et al¹¹ in London who analyzed retrospective data from 80 cases born in the United Kingdom. This study showed that 13% of the children were anemic at birth and 72.5% had presented by the age of 3 months.

All cases of transient erythroblastopenia of childhood presented between 1–4 years of age. Yska et al¹² in Zwolle showed that transient erythroblastopenia of childhood affects children between the age of 1 and 4 years. But it is also seen in rare cases in older children as Sharma et al¹³ presented primary acquired pure red cell aplasia in an 11 year old child in India.

The male to female ratio in pure red cell aplasia in our study was about 1:1.5. The Diamond Blackfan

anemia showed the male: female of about 1:1.5 and in transient erythroblastopenia of childhood it was found to be 1:1.3. Ball et al¹¹ in London showed a male: female of 1:1.4. Similarly, Ohga et al¹⁴ in Japan showed slight female predominance with a male: female of 1:1.07 in Diamond Blackfan anemia. Sex distribution in transient erythroblastopenia of childhood was not found to be significant as it almost equally affects both males and females.

The common presenting complaint in Diamond Blackfan anemia was found to be pallor which was present in all cases (100%), followed by fever in 52.1% of cases, failure to thrive in 21.7% of cases, respiratory distress in 8.6% of children. About 91.3% of the children received blood transfusions. On examination height and weight was below 3rd centile in 26% of cases, pallor was present in 100% of cases, physical anomalies were present in 43.4% of children (60% have craniofacial dysmorphism, 40% have thumb anomalies), mild hepatomegaly and mild splenomegaly was seen in about 8.6% and 13% of cases respectively in present study. Manglani et al¹⁵ in India reported 16 children with Diamond Blackfan anemia, all had severe pallor at presentation with mild hepatomegaly and just palpable spleen in one of them (16%). Thumb anomaly was present in one of them (16%). Similarly Ball et al¹¹ in London demonstrated physical anomalies in 37% of patients and height was below the 3rd centile for age in 28%.

The history and physical examination in transient erythroblastopenia of childhood showed that the children presented always with anemia associated sometimes with fever. There were no other significant physical findings. Yska et al¹² in Zwolle showed that apart from anemia other symptoms are rare in transient erythroblastopenia of childhood.

The investigations in Diamond Blackfan anemia in this study revealed a mean red blood cell count of $1.88 \times 10^{12}/L$, mean hemoglobin concentration of 4.97 g/dl and mean reticulocyte count of about 0.27. About 82.6% of patients had normocytic normochromic blood picture while rest of the children (17.3%) had macrocytic normochromic blood picture. Bone marrow examination revealed either absent or markedly reduced erythropoiesis. El-Beshlawy et al⁽¹⁶⁾ revealed in their study in Egypt a mean hemoglobin concentration of 4.75g/dl and a mean reticulocyte count of 0.14.

The investigations in transient erythroblastopenia of childhood revealed the mean red blood cell count of $2.01 \times 10^{12}/L$, mean hemoglobin concentration of 5.44 g/dl and mean reticulocyte count of about 0.21. Bone marrow examination showed marked erythroid hypoplasia in the present study. Tourniaire et al¹⁷ in France showed a mean

hemoglobin level of 4 – 6.7 g/dl in 6 patients along with profound erythroblastopenia on bone marrow examination in them.

Most patients had no or very few erythroid elements whereas some patients retain a relatively normal number of erythroid precursors with an arrest at the proerythroblast stage. These stages in erythroid development require different molecules including transcription factors and proteins in the erythropoietin signaling pathway that may be involved in the pathogenesis of Diamond Blackfan anemia. The critical region responsible for the pathogenesis of Diamond Blackfan anemia has been mapped in some patients to chromosome 19q13.2 and the gene encoding ribosomal protein S 19 (RPS 19) is believed to be the candidate gene. The limitations of the present study include the non - availability of molecular / cytogenetic analysis along with adenosine deaminase levels which are important in differentiating Diamond Blackfan anemia with transient erythroblastopenia of childhood.

CONCLUSIONS

It was found to be more common than Transient Erythroblastopenia of childhood in all the children with pure red cell aplasia. Females were affected more than the males in Diamond Blackfan anemia but transient erythroblastopenia of childhood was found almost equally in both sexes. Most of the children with Diamond Blackfan anemia presented by the age of 3 months while transient erythroblastopenia of childhood occurred between 1–4 years of age. Anemia without lymphadenopathy and hepatosplenomegaly were salient clinical features. Congenital anomalies were seen in 43.4% of patients of Diamond Blackfan anemia. RBC count, hemoglobin concentration, reticulocyte count and bone marrow examination were the main investigations in diagnosing pure red cell aplasia in children.

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