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Original Research Article

Non-nutritional causes of severe anemia in Kashmiri children

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ABSTRACT

Background: Anemia is one of the leading causes of mortality and morbidity in children. The etiology of anemia is multifactorial including nutritional anemia, hemolytic anemia, aplastic anemia, storage disorders, hematological malignancies, anemia secondary to some chronic diseases.
Methods: The study is an observational study. Physical signs of severe anemia were looked in patients attending outpatient department or admitted in hospital. Children with hemoglobin levels <7 g/dl and in the age group 6 months to 6 years were recruited in study. The aim is to look for non-nutritional etiology of severe anemia in children in Kashmir.
Results: Out of 192 children, 97 (50.52%) females and 95 (49.48%) males, with a male, female ratio of around 1:1. A total of 147 (76.56%) children in our study were having nutritional and 45 (23.44%) were having non nutritional causes. Among non-nutritional anemia 30 cases were hemolytic anemia, 11 hypoplastic anemia, 3 leukemia and 1 patient were diagnosed as Osteopetrosis.
Conclusions: Though nutritional deficiency anemias are predominant; it may not always be the case. Hemolytic anemia and leukemias should be ruled out while evaluating a patient of severe anemia and pancytopenia. Bone marrow failure syndrome, storage disorders should be ruled out in patients with skeletal anomalies.

Keywords: Hypoplastic anemia, Gaucher's disease, Osteopetrosis, Severe anemia, Reticulocytes

INTRODUCTION

The world health organization estimates that around two billion individuals worldwide are anemic, highlighting the importance of anemia as a public health issue in both developing and developed nations.[1,2] Anemia is one of the leading causes of mortality and morbidity in children.[3] Clinically severe anemia is characterized by palmar pallor, conjunctival pallor, pallor in nail beds and mid systolic flow murmur chiefly in pulmonic area due to increased flow across heart valves. Severe anemia is characterized by high output state with elevated pulse pressure and collapsing pulse. Severe anemia may precipitate heart failure even with normal cardiovascular system.[4] The etiology of anemia is multifactorial including nutritional anemia, hemolytic anemia, aplastic anemia, hematological malignancies, anemia secondary to some chronic diseases and others.[5] Statistics published in the United States show iron deficiency prevalence rates of 9% in girls of 12 to 15 years of age and 16% in girls aged 16-19 years. In boys, these rates are lower.[6] In developing countries, the situation is more serious. In India, a prevalence of anemia of 45% has been reported for teenage girls.[7] In Indonesia, prevalence rates were 26% and 11 % for girls and boys, respectively.[8] In Jamaica, anemia was identified in 25% of adolescents of 12 to 15 years of age.[8] Nutritional anemia is the most common cause with iron deficiency anemia leading the list. Apart from nutritional causes there are many non-nutritional causes like congenital hypoplastic

anemia, hemolytic anemia, storage disorders and leukemias especially in severely anemic children.

METHODS

This is an observational study and was conducted in GB Pant hospital, an associated tertiary care hospital of GMC Srinagar from September 2016 to September 2020 after clearance from ethical committee of GMC Srinagar. Signs of severe anemia like conjunctival pallor, palmar pallor and mid systolic murmur were looked in patients attending outpatient department or admitted in hospital. Confirmation of clinically severe anemia was done by laboratory estimation of hemoglobin levels. After taking informed consent from parents, 2ml sample was drawn from peripheral venipuncture site after taking all aseptic precautions. Patients with hemoglobin less than 7 g/dl were recruited in study. The aim of the study was to look for non-nutritional causes of severe anemia in children in the age group 6 months to 6 years.

Inclusion criteria

Inclusion criteria for current study were; children in the age group 6 months to 6 years with hemoglobin levels <7g/dl with no history of blood transfusion within previous three months.

Exclusion criteria

Exclusion criteria for current study were; children already on treatment for anemia.

Statistical analysis

Data was entered in Microsoft excel spreadsheet analyzed using Epi INFO. Categorical variables were summarized as frequency and percentage. Continuous variables were summarized as mean and standard deviation or as five number (minimum, 1st quartile, median, 3rdquartile, maximum).

RESULTS

The study included 192 patients who fulfilled the inclusion criteria. It included 97 (50.52%) females and 95 (49.48%) males, with a male, female ratio of around 1:1 as depicted in (Table 1). The most common presentation in our study group was fever which was present in 86 cases (44.77%), followed by diarrhea and easy fatigability which were present in 38 (19.79%) and 21 (10.93%) patients respectively. The less common presentations were jaundice, gastrointestinal bleeding, cough and vomiting which were present in 14 (7.29%), 12 (6.25%), 11 (5.72%) and 10 (5.20%) patients respectively as depicted in (Table 2). On examination pallor was seen in all patients, followed by hemolytic facies, knuckle pigmentation, jaundice, glossitis, and splenomegaly which were seen in 22, 22, 14, 13 and 12 respectively.

Table 1: Gender distribution.

Gender	N	%
Male	95	49.48
Female	97	50.52
Grand total	192	100.00

Table 2: clinical presentation of study subject.

Symptoms	N	%
Fever	86	44. 77
Diarrhea	38	19. 79
Easy fatigability	21	10. 93
Jaundice	14	7. 29
GI Bleeding	12	6. 25
Cough	11	5. 72
Vomiting	10	5. 20

The other findings were koilonychia, hepatomegaly, microcephaly, micrognathia, petechia, hypertelorism, lymphadenopathy, café-au- lait spots, triphalangeal thumb, absent thumb and radius, and bone tenderness s shown in (Figure 1).

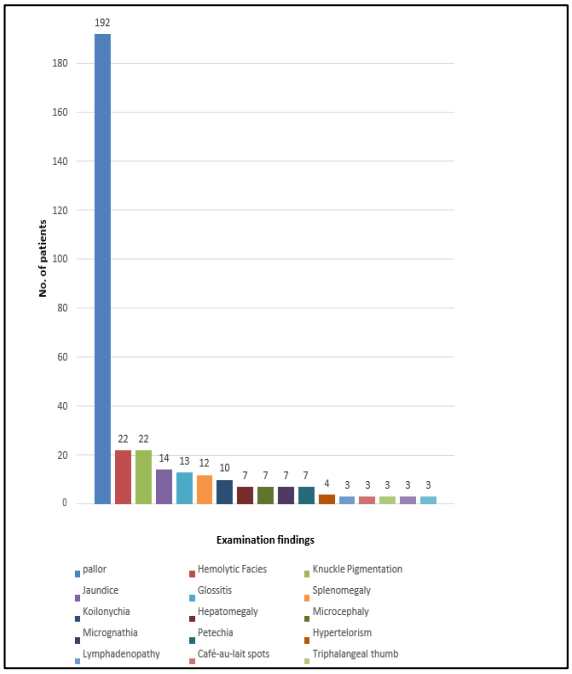

Figure 1: Examination findings in patients with severe anemia.

After detailed history, examinations and investigations 115 (59.90%) patients were diagnosed with iron deficiency anemia, proving to be the predominant etiology in our study. 19 cases were diagnosed as Megaloblastic anemia. 13 cases were diagnosed as dual deficiency anemia. 30 cases were diagnosed as hemolytic anemia, 11 cases were diagnosed as hypoplastic anemia. 3 cases were diagnosed as acute lymphoblastic leukemia. Table 3 below depicts a detailed etiology of all the cases.

Table 3: Distribution of etiology (n=147).

Nutritional anemia	N	%	% within group
Iron deficiency	115	59.90	78.23
Megaloblastic anemia	19	9.90	12.93
Folate deficiency	3	1.56	15.79
Vitamin B12+folate deficiency	12	6.25	63.16
Vitamin B12 deficiency	4	2.08	21.05
Dual deficiency	13	6.77	8.84
Vitamin B12+iron deficiency	8	4.17	61.54
Folate+iron deficiency	5	2.60	38.46
Non-nutritional anemia	45	23.44	-
Hemolytic Anemia	30	15.63	66.67
Autoimmune hemolytic anemia	8	4.17	26.67
Beta thalassemia	10	5.21	33.33
Hereditary spherocytosis	12	6.25	40.00
Hypoplastic Anemia	11	5.73	24.44
Diamond Blackfan anemia	4	2.08	36.36
Fanconi's anemia	3	1.56	27.27
Gaucher's disease	4	2.08	36.36
Others	4	2.08	8.89
Acute lymphoblastic leukemia	3	1.56	75.00
Osteopetrosis	1	0.52	25.00
Grand total	192	100	-

Table 4: Distribution of hemolytic anemia (n=30).

Hemolytic Anemia	N	%
Hereditary spherocytosis	12	6. 25
Beta thalassemia	10	5. 21
Autoimmune hemolytic anemia	8	4. 17

Table 5: Age distribution of hemolytic anemia patients (n=30).

Hemolytic Anemia	N	%
Autoimmune hemolytic anemia	8	4. 17
49 to 72 Months	6	3. 13
19 to 48 Months	2	1. 04
Beta thalassemia	10	5. 21
6 to 18 Months	9	4. 69
19 to 48 Months	1	0. 52
Hereditary spherocytosis	12	6. 25
6 to 18 Months	6	3. 13
49 to 72 Months	2	1. 04
19 to 48 Months	4	2. 08

Etiology of non-nutritional anemia

In our study 30 cases were diagnosed with hemolytic anemia. Hemolytic facies were found in 22 patients and jaundice was found in 14 patients and splenomegaly in 5 patients. PBF showed nucleated RBCs with red cell fragments suggestive of hemolytic anemia. Retic count was on higher side and retic index was >2 in all cases. Subsequently all patients were evaluated on the lines of hemolytic anemia. HB electrophoresis, osmotic fragility, G6PD and DCT was done. HB electrophoresis showed increased fetal hemoglobin levels (Hb-F) in 10 patients suggestive of beta thalassemia. Osmotic fragility was increased in 12 patients suggestive of hereditary spherocytosis. DCT was positive in 8 patients suggestive of autoimmune hemolytic anemia. In 2 patients of autoimmune hemolytic anemia peripheral blood film showed RBC clumps suggestive of cold autoimmune hemolytic anemia. IgM mycoplasma pneumoniae was positive in these 2 cases. Both these cases belonged to age group (19-48 months).

Table 6: Frequency of hypoplastic anemia (n=11).

Hypoplastic Anemia	N	%
Diamond black fan anemia	4	2. 08
Fanconi's anemia	3	1. 56
Gaucher's disease	4	2. 08

In 2 cases of autoimmune hemolytic anemia ANA and anti dsDNA antibodies were positive and were diagnosed as SLE, both these cases belonged to age group (49-72 months). In remaining 4 patients of autoimmune hemolytic anemia ANA levels, monospot IgM mycoplasma pneumoniae and bone marrow examination were done. All these investigations were normal and there was no history of preceding drug intake in these patients, and hence these 4 patients were labeled as idiopathic autoimmune hemolytic anemia. All these 4 patients belonged to age group (49 to 72 months). The description of hemolytic anemia is depicted in the (Table 4-5).

Observations of hypoplastic anemia

In our study 4 cases were diagnosed as diamond black fan anemia. These patients were having microcephaly, micrognathia, hypertelorism, triphalangeal thumb and broad nasal bridge. PBF showed macrocytic RBCs but no hypersegmented neutrophil. Retic count was found to be very low and retic index was <0.7 in all cases. Serum iron, ferritin, TIBC, vitamin B12 and folic acid levels were normal. Bone marrow examination was done in these patients and showed markedly decreased erythrocyte precursors suggestive of diamond black fan anemia. 3 cases were diagnosed as Fanconi's anemia. On examination these patients were found to have microcephaly, micrognathia, café-au- lait spots, epicanthal folds and absent thumb and radius. CBC, PBF and retic count was done. CBC showed pancytopenia. Retic count was on lower side and retic index was <1. Bone marrow examination was done and showed features of hypoplastic marrow. Subsequently chromosomal breakage study was done, which was positive in all these cases. Four cases were diagnosed as Gaucher's disease. These patients had developmental delayed hepatosplenomegaly and petechial lesions. CBC showed pancytopenia. Retic index was <1 in

all these cases. Bone marrow examination showed Gaucher's cells diagnostic of Gaucher's disease. Enzyme assay revealed decreased beta glucosidase levels. Three cases were diagnosed as acute lymphoblastic leukemia. These patients were found to have hepatosplenomegaly bone tenderness and petechial lesions. CBC showed pancytopenia and PBF showed blasts. Bone marrow was done which showed >30% lymphoblasts. One patient was diagnosed as osteopetrosis. This patient was found to have hepatosplenomegaly and macrocephaly. Infantogram showed generalized increased in bone density suggestive of osteopetrosis.

DISCUSSION

Our study included 192 patients who fulfilled inclusion criteria. Out of 192 patients, 97 were males and 95 were females with male to female ratio of 1 :1. Majority of patients in our study were in age group 6 to 18 months (54%). The most common etiology in our study was nutritional (76.56%) and 23.44% were having non nutritional causes. Among nutritional causes iron deficiency anemia is most common (59.9%). Out of 115 patients of iron deficiency, 85 had inadequate iron and calorie intake and 30 patients had adequate calorie intake. Among these 30 patients 14 had underlying celiac disease, 10 had trichuriasis, 4 had cow milk protein allergy and 2 had rectal polyp. Megaloblastic and dual deficiency anemia was seen in 19 (9.9%) and 13 (6.77 %) cases respectively. These patients had knuckle pigmentation and glossitis. Among non-nutritional causes, hereditary spherocytosis was seen in 12 cases (6.25%). Hereditary spherocytosis is the most commonly seen hemolytic anemia in Kashmir. In many other studies hereditary spherocytosis was not seen as cause of severe anemia. This is probably due to the fact that overall worldwide prevalence of hereditary spherocytosis is low. Thalassemia was seen in 10 cases (5.21%). Thalassemia is very rare in Kashmir. Out of these 10 patients 5 patients were hailing from Uttar Pradesh whose parents were working here, 3 patients were from Rajouri and 2 patients were from Uri Baramulla. Kavya Bharathidasan et al in their study found thalassemia in 3.3% patients.[9] Srinivas Madoori et al reported thalassemia in 9% patients.[10] In our study autoimmune hemolytic anemia was seen in 8 cases (4.1%), out of these 4 cases (50%) had idiopathic autoimmune hemolytic anemia and 4 cases (50%) had secondary autoimmune hemolytic anemia. Out of 4 cases of secondary autoimmune hemolytic anemia, 2 had systemic lupus erythematosus and 2 were positive for IgM mycoplasma pneumonia. In study by Naithani et al on autoimmune hemolytic in children, idiopathic autoimmune hemolytic was seen in 65% cases and secondary autoimmune hemolytic was seen in 35% cases.[11] We found diamond black fan in 4 cases (2.08%). These patients had skeletal anomalies like triphalangeal thumb, hypertelorism and micrognathia. Gaucher's disease was seen in 4 cases (2.08%). These patients presented with global developmental delay and hepatosplenomegaly. In our study Fanconi's anemia was seen in 3 cases (1.56%). These patients had short stature, café-au-lit spots and skeletal anomalies like absent thumb and radius, microcephaly and micrognathia. Acute lymphoblastic leukemia was seen in 3 cases (1.5%). These patients had hepatosplenomegaly, petechial lesions and bone tenderness. Taniya Sarkar Dutta et al found acute lymphoblastic leukemia in 1% patients.[12] Osteopetrosis was seen in one patient (0.5%). In other studies, osteopetrosis was not seen. This is probably due to the fact that osteopetrosis is very rare disease.

Limitations

Limitations of current study were; mild and moderate anemic patients were not included in the study and there was recall bias on dietary history.

CONCLUSION

Though nutritional deficiency anemias are predominant, it may not always be the case. Thorough diagnostic works up is needed to accurately diagnose the cause and to administer effective and relevant treatment. Hemolytic anemia and leukemias should be ruled out while evaluating a patient of severe anemia. Bone marrow failure syndrome should be ruled out in patients having skeletal anomalies.

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