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Original Research Article

Etiology of severe anemia in Kashmiri children aged 6 months to 6 years

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ABSTRACT

Background: Anemia is said to be present when the hemoglobin level is more than two standard deviations below the mean for the child's age and sex. Anemia is the most common global nutritional disorder and may lead to psychomotor retardation, low intelligence, decreased learning capability, weakening of immune system and predisposes to serious infections in children.
Methods: The study was an observational study. Physical signs of severe anemia were looked in patients attending outpatient department or admitted in hospital. Children with hemoglobin levels <7 gm/dl and in the age group 6 months to 6 years were recruited in study.
Results: The study included 192 patients with a male, female ratio of around 1:1. The mean age of the study subjects was 2.2±1.6 years. Most of the patients around 54% belonged to age group of 6 months to 1½ years. Fever was most common presentation in 86 cases (44.77%), followed by diarrhea and easy fatigability in 38 (19.79%) and 21 (10.93%) patients respectively. A total of 76.56% of patients were having nutritional and 23.44% non-nutritional causes. Iron deficiency anemia is most common etiology 115 (59.90%) with 14 patients having celiac disease, 19 cases (9.90%) were diagnosed as megaloblastic anemia, 13 cases (6.77%) were diagnosed as dual deficiency anemia, 30 cases (15.63%) were diagnosed as hemolytic anemia.
Conclusions: Nutritional anemia is major cause of anemia in children. Celiac disease, trichuriasis, cow milk protein allergy should be ruled out in iron deficiency anemia patients.

Keywords: Celiac disease, Dual deficiency, Iron deficiency, Trichuriasis

INTRODUCTION

Anemia is said to be present when the hemoglobin levels is more than two standard deviations below the mean for the child's age and sex.[1] According to WHO anemia is defined as when hemoglobin levels are below 11 gm/dl in children between 6 months to 6 years and below 12 gm/dl in children 6 years to 12 years of age.[2]

In normal individuals, hematocrit and hemoglobin levels vary in accordance with the phase of development of the individual, and as a function of hormonal stimulation, environmental oxygen pressure, age and gender.[3] As per WHO anemia is said to be severe when the hemoglobin level is less than 7 gm/dl.[4] Anemia is commonest problem in growing age group in developing countries.[5,6] Anemia is the most common global nutritional disorder and affects 1.62 billon people worldwide.[7] Anemia is one of the leading causes of mortality and morbidity in school children.[8]

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.[1]

According to the national family health survey for the year 2005-2006 an alarming 78.9% of children in India between the ages of 6-35 months were found to be anemic.[9] When anemia is sufficiently severe it has negative health impacts in growing children and adolescents.[10,11] Different studies in Egypt, India, Thailand and United States have shown that severe anemia in children is accompanied by psychomotor retardation, low intelligence and decreased learning capability.[12-15] Anemia results in decrease in oxygen carrying capacity of blood. Severe anemia results in weakening of immune system and predisposes to serious infections.[16,17]

The etiology of anemia is multifactorial including nutritional anemia, hemolytic anemia, aplastic anemia, hematological malignancies, anemia secondary to some chronic diseases and others.[18] Various factors influence the incidence of anemia such as whether child was breastfed or formula fed duration of breast feeding (both exclusive and complementary) the age at which child starts weaning as well as iron content of foods first introduced.[19-22]

METHODS

This was 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, 2 ml sample was drawn from peripheral venipuncture site after taking all aseptic precautions. Patients with hemoglobin less than 7 gm/dl were recruited in study.

Inclusion criteria

Children in the age group 6 months to 6 years with hemoglobin levels <7 gm/dl with no history of blood transfusion within previous three months.

Exclusion criteria

Children with known coagulation disorders and on treatment for anemia.

Statistical analysis

Data was entered in Microsoft excel spreadsheet analysed 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, 3rd quartile, 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. The mean age of the study subjects was 2.2±1.6 years. Most of the patients belonged to age group of 6 months to 1½ years consisting of 104 patients (54.17% of total patients), followed by age group of 4 to 6 years consisting of 49 patients (25.52% of total patients). The least number of patients belonged to age group of 1½ to 4 years, consisting of 37 patients (19.27% of total patients). Age distribution is further elaborated in Table 1.

Table 1: Age distribution.

Age group	No. of cases	Percentage
6 to 18 months	104	54.17
Male	57	29.69
Female	47	24.48
1½ to 4 years	39	20.31
Male	18	9.38
Female	21	10.94
4 to 6 years	49	25.52
Male	20	10.42
Female	29	15.10
Total	192	100.00

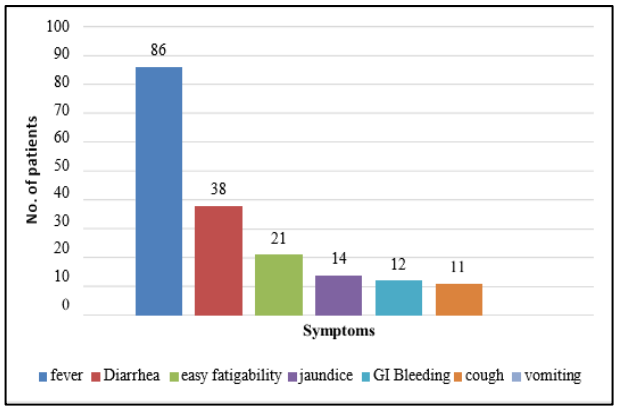

Figure 1: Clinical presentation of study subject.

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 Figure 1.

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. The other findings were koilonychia, hepatomegaly, microcephaly, micrognathia, petechia, hypertelorism, lymphadenopathy, café-au-lait

spots, triphalangeal thumb, absent thumb and radius, and bone tenderness as shown in Table 2. The mean hemoglobin level of the study population was 5.12±0.94 gm/dl with a minimum and maximum of 3.51 gm/dl and 6.87 gm/dl respectively. 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. 30 cases were diagnosed as hemolytic anemia. 19 cases were diagnosed as megaloblastic anemia. 13 cases were diagnosed as dual deficiency anemia 11 cases were diagnosed as hypoplastic anemia. 3 cases were diagnosed as acute lymphoblastic leukemia as shown in Figure 2.

Table 2: Examination findings.

Findings	No. of cases	Percentage
Pallor	192	100
Hemolytic facies	22	11.46
Knuckle pigmentation	22	8.33
Jaundice	14	7.29
Glossitis	13	6.7
Splenomegaly	12	6.25
Koilonychia	10	5.2
Hepatomegaly	7	3.65
Microcephaly	7	3.65
Micrognathia	7	3.65
Petechia	7	3.65
Hypertelorism	4	2.08
Lymphadenopathy	3	1.56
Café-au-lait spots	3	1.56
Triphalangeal thumb	3	1.56
Absent thumb and radius	3	1.56
Bone tenderness	3	1.56
Grand total	192	100

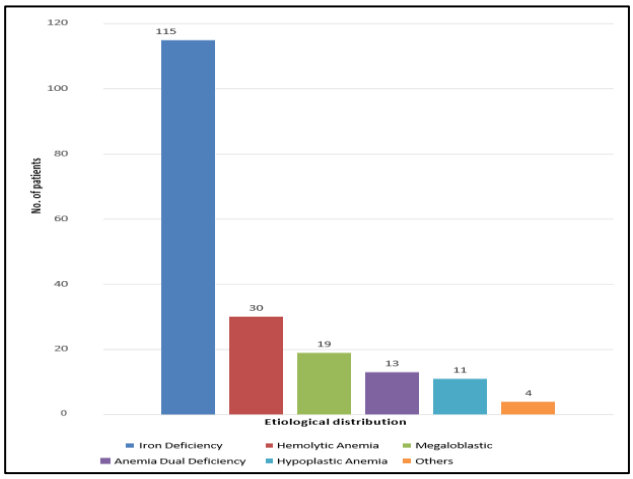

Figure 2: Etiology of anemia.

Results and observations related to iron deficiency

In our study 115 (59.90%) patients out of 192 patients were diagnosed as iron deficiency anemia proving to be the predominant etiology in our study. After detailed dietary history 85 of these patients were found to have significantly low calorie and iron intake and 30 patients had adequate calorie and iron intake. Among these 30 patients, 14 patients had history of diarrhea and abdominal distention, 10 patients had bloody diarrhea, 4 patients presented with non-bloody diarrhea and 2 patients had frank per rectal bleeding. It was found that 26 (22.61%) patients were exclusively breast fed till first six months of life, 28 (24.35%) patients were on cow's milk and 61 (53.04) patients were on mixed feeding. The average age at which complementary feeds were started was 9.5 months. Feeding till initial six months of life in iron deficiency anemia patients is depicted in table 3. CBC and PBF showed features of microcytic hypochromic anemia and retic count was too low for the degree of anemia and retic index was <0.81 in all cases. Subsequently serum iron, TIBC and serum ferritin levels done, which were significantly low in all these patients. Stool for occult blood was positive in 4 cases. Celiac serology (IgA tTG and IgA dGP) was done in 14 patients who presented with diarrhea and abdominal distention and was found positive. Subsequently, upper GI endoscopy was done in these 14 patients and duodenal biopsies were taken and were sent for histopathological examination. Upper gastrointestinal endoscopy showed loss of mucosal folds and mucosal atrophy. Histopathological examination revealed villous atrophy and increase in intraepithelial lymphocytes suggestive of celiac disease.

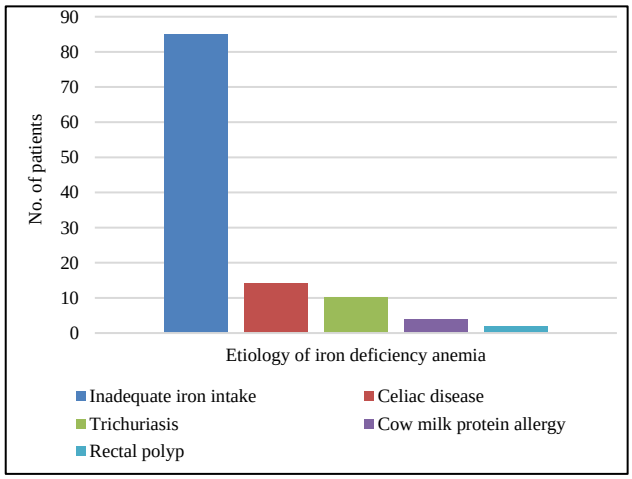

Figure 3: Etiology of iron deficiency anemia.

Colonoscopy was done in 10 patients who presented with bloody diarrhea and showed multiple *Trichuris trichiura* in sigmoid colon and rectum. Stool examination was done in these patients which was positive for Trichuris eggs. Stool for occult blood was positive in 4 patients who presented with diarrhea without abdominal distention. In these 4 patients colonoscopy was done and showed multiple aphthous ulcers and nodular lymphoid hyperplasia in sigmoid colon and rectum. Colonoscopic biopsy was done in these patients which showed crypt abscess with eosinophilic infiltration. These patients had

personal as well as family history of atopy. These 4 patients were on cow's milk right from birth and belonged to age group 6 months to 1½ year. Cow's milk was eliminated from their diet and there was significant improvement in diarrhea after withdrawal of cow's milk and were diagnosed as cow's milk protein allergy. In 2 patients who presented with frank bleeding per rectal, colonoscopy revealed rectal polyps. The etiology of iron deficiency anemia is depicted in Figure 3.

Results and observations of megaloblastic anemia

In our study 19 patients were diagnosed as megaloblastic anemia. After detailed history examination including dietary history these patients were found to have significantly low-calorie intake and were predominantly on vegetarian diet. On examination knuckle pigmentation was found in 16 patients and glossitis was seen in 8 patients. CBC showed macrocytic anemia. PBF revealed macrovalocytes with hypersegmented neutrophils. Subsequently vitamin B_{12} and folic acid levels were done in all patients. Both vitamin B_{12} and folate levels were low in 12 patients. Only vitamin B_{12} deficiency was seen in 4 patients. Similarly, only folate deficiency was seen in 3 patients as shown in Table 3.

Table 3: Etiology of megaloblastic anemia.

	N	%
Megaloblastic anemia	19	9.90
Vitamin B_{12} + folate deficiency	12	6.25
Vitamin B_{12} deficiency	4	2.08
Folate deficiency	3	1.56

Results and observations in dual deficiency

In our study 19 patients were diagnosed as dual deficiency anemia. On history including dietary history calorie intake was significantly low in all the patients. On examination 5 patients had glossitis and 6 patients had knuckle pigmentation. CBC, PBF and retic count was done in all the patients. PBF showed dimorphic picture both microcytic, hypochromic and macrovalocytes were seen. Retic count was significantly low and retic index was <0. 8 in all patients. Subsequently serum iron, TIBC, ferritin, vitamin B_{12} and folate levels were done. Both folate and iron deficiency were found in 5 patients. Similarly, vitamin B_{12} and iron deficiency was found in 8 patients as shown in Table 4. Stool for occult blood, ova cysts and parasites were negative in all the patients.

Table 4: Dual deficiency.

	N	%
Dual deficiency	13	6. 77
Dual deficiency (folate + iron deficiency)	5	2. 60
Dual deficiency (vitamin B_{12} + iron deficiency)	8	4. 17

DISCUSSION

Our study included 192 patients, out of which 97 were males and 95 were females. In our study majority of patients belonged to age group 6-18 months. Out of 192 patients, 104 (54.1%) were in age group 6-18 months. Saba et al conducted study on anemia in children between 6 months to 12 years at Bangalore, Karnataka and they found that most affected age group was between 6 months to 1 year.[23] Akin et al found that hemoglobin and hematocrit of patients with age 6 to 24 months was significantly lower than those of patients with age of more than 24 months.[24] Sinha et al conducted a study for screening of anemia among children (6-35 months) in rural Wardha Maharashtra and found that out of 772 children included in the study, 18.8% children were 6 to 11 months of age and 40% were 12 to 23 months of age.[25] The higher prevalence of anemia in children less than 2 years could be attributed to delayed introduction of complementary feeds and inadequate complementary feeds resulting in calorie and iron deficit. The most common presenting symptom in our study was fever in 86 cases (44.79%) followed by diarrhea in 38 cases (19.79%). Venkatesh et al in their study found fever in 59% patients and diarrhea in 16.3% patients similar to our study.[26] The most common etiology in our study was iron deficiency anemia. Out of 192 patients, 115 patients were iron deficiency anemia (59.9%). Similar results were seen in many other studies. Venkatesh et al in their study found iron deficiency anemia in 54.4% of patients.[26] In study done by Madoori et al at Chalmeda Anand Rao institute of medical sciences Telangana, iron deficiency was seen in 58% of patients.[27]

In our study 85 patients of iron deficiency had inadequate calorie and iron intake and 30 patients had adequate calorie and iron intake. Among these 30 patients, 14 patients were diagnosed as celiac disease. These patients presented with chronic diarrhea and abdominal distension. Manish Narang et al in their cross-sectional study found that celiac disease accounted for 8.5% and 3.9% of children with severe and moderate to severe iron deficiency anemia respectively.[28]

Worm infestation by *Trichuris trichiura* accounted for 10 cases (8.7%) of iron deficiency anemia in our study. These patients presented with diarrhea and blood in stools. Colonoscopy in these patients revealed multiple Trichuris worms in sigmoid colon. Trichuriasis is an established cause of anemia in children similar to Quihi et al.[29]

Cow milk protein allergy was seen in 4 cases of iron deficiency anemia and accounted for 3.48% of iron deficiency anemia in our study. Cow's milk was eliminated from their diet and there was substantial improvement subsequently similar to results by Lai et al.[30] Megaloblastic anemia was seen in 19 patients (9.89%). These patients had knuckle pigmentation and

glossitis similar to results of Dutta et al and Madoori et al.[27,31]

CONCLUSION

Nutritional anemia is major cause of anemia in children. This can be prevented by exclusive breastfeeding till six months of age, introduction of complementary feed at appropriate time and in adequate quantity and quality. Celiac disease should be ruled out in iron deficiency anemia patients where there is history of chronic diarrhea, abdominal dissension and poor response to iron therapy. Trichuriasis should be ruled out in iron deficiency anemia patients presenting with diarrhea and blood in stools. Cow milk protein allergy should be ruled out in patients of iron deficiency who are on cow's milk and have personal or family history of atopy and poor response to iron therapy. Diet rich in vitamin B^{12} and folate should be provided to prevent megaloblastic and dual deficiency anemia. Though nutritional deficiency anemias are predominant, it may not always be the case. Hemolytic anemia should be ruled out while evaluating a patient of anemia.

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