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A clinico-hematological study of severe anemia in hospitalized children aged 6 months to 12 years in a tertiary care institute from North India: An observational study

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Abstract: *Background:* Anemia is a global health problem, more so in low- and middle-income countries (LMIC) like India. Prevalence of anemia in children is rising in recent years, as reflected by National Family Health Survey - 5 data (2019-21), despite many government programs for its prevention. If not diagnosed and treated timely, these children may land up into severe anemia, which frequently requires blood transfusion. *Purpose:* To understand severe anemia in children, in a better way, which may be helpful in chalking out preventive and therapeutic strategies. *Methods:* Hospitalized children aged 6 months to 12years, having severe pallor on clinical examination were included. Apart from history taking and clinical examination, complete blood counts (including hemoglobin) along with other relevant investigations were done on venous blood. Severe anemia was defined as Hb < 7 g/dl in children aged 6-59 months and Hb < 8 g/dl in children aged 5-12 years as per WHO criteria. *Result:* Commonest age group of severe anemia children was 6 months-2years. Risk factors included low birth weight, younger age, lower socioeconomic status, improper feeding practices with lesser consumption of iron rich food and malnutrition. Majority presented with symptoms of respiratory tract infection and elevated body temperature at the time of admission. Maximum cases had microcytic hypochromic anemia. Iron deficiency anemia was found to be the commonest cause of severe anemia in 45% cases. Severe acute malnutrition is associated with a relatively lower level of hemoglobin of <5 gm/dl. *Conclusion:* Severe anemia is more common in under 5-year children. Early diagnosis of severe anemia with clinical and basal blood parameters, along with its etiology is essential before start of treatment, to avoid unwanted side effects e.g., iron overload. Anemia is frequently associated with malnutrition, so there is a need for parental counselling for child feeding practices, apart from ongoing deworming and iron-folic acid supplementation programs by the government.

Keywords: Severe Anemia, Children, Hemoglobin, Malnutrition.

Introduction

Anemia is a major global health problem, especially in low- and middle-income countries (LMIC) like India, despite being preventable and easily treatable. As per National Family Health Survey (NFHS-5, 2019-21), 67.1% children aged 6 to 59 months were found to be having some degree of anemia (hemoglobin <11 gm/dl), out of which mild, moderate and severe anemia was found in 29%, 36% and 2.1% respectively [1].

The prevalence of anemia is rising across all age groups (58.6% in NFHS-4, year 2015-16 **vs** 67.1% in NFHS-5, year 2019-21, in children aged 6-59 months), despite the fact that many programs have already been launched by government of India to prevent it. According to WHO estimates (year 2019), global prevalence of anemia was 39.8% in children aged 6-59 months, equivalent to 269 million children with anemia [2].

Various risk factors include age, sex, family size, poor maternal education and health status, low family income, inadequate sanitary conditions, lack of access to healthcare services, low birth weight, prematurity, malnutrition and diet with insufficient amount

of iron, consumption of cow milk before 6 months of age, early or late introduction of complementary feeds and parasitic infestations [3-4]. Common causes of anemia are nutritional deficiencies, infectious and inflammatory diseases and genetic hemoglobin disorders. Early recognition and treatment of anemia is of crucial importance as anemia is associated with negative short- and long-term effects on child's physical, mental and social growth. It also results in abnormal immune function, poor motor and cognitive growth, poor academic performance, decreased work productivity and increased susceptibility to infections which lowers individual's earning potential, thereby impacting nation's economic growth.

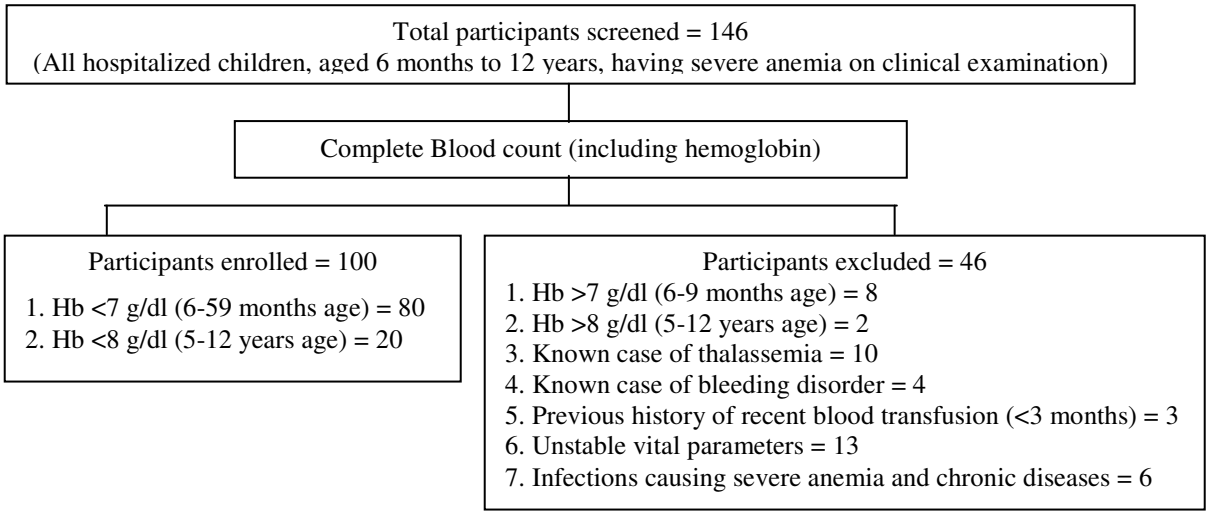
There are many studies on anemia per se in Indian children, but very few studies focus on *severe anemia*. Mild to moderate anemia can be corrected by appropriate nutrition and treating the cause, but severe anemia is usually transfusion dependent. Grouped and cross matched blood is difficult to acquire many a times, as there are few donors and shelf life of blood is limited. Additionally, there is a risk of acquiring transfusion - transmitted infection through blood. Morbidity and mortality rates are also higher in severe anemia as compared to mild and moderate anemia. In view of magnitude and consequences of severe anemia, this study was planned with the aim to identify various risk factors, clinical profile and hematological parameters in children (age 6 months to 12 years), with severe anemia in a better way which may be helpful in chalking out preventive and therapeutic strategies to reduce morbidity and mortality associated with severe anemia.

Material and Methods

This cross-sectional observational study was conducted in department of Pediatrics, government medical college, Prayagraj over a span of one year. Institutional ethical clearance was taken prior to start of study. All hospitalized children in the age group 6 months to 12 years, who had severe pallor on clinical examination (according to Integrated Management of Neonatal and Childhood Illness i.e. IMNCI guidelines for assessment of pallor) [5] were screened and investigated for level of hemoglobin (Hb) by sending complete blood count (CBC) in the laboratory. Those children whose Hb level was in the range of severe anemia were enrolled for study, after taking parental consent, till sample size was reached. Severe anemia was defined as Hb < 7 g/dl in children aged 6-59 months and Hb < 8 g/dl in children aged 5-12 years as per WHO criteria [6].

Children excluded were those who were known case of thalassemia, leukemia or bleeding disorder (e.g., hemophilia, immune thrombocytopenic purpura)/ who had history of blood transfusion in recent past i.e., within past 3 months/ having congenital malformation/ having unstable vital parameters/ suffering from infections causing severe anemia e.g., dengue, malaria, HIV/ chronic disease e.g., chronic kidney disease (CKD) or chronic liver disease (CLD). Fig-1 depicts recruitment of patients in the study.

Fig-1: Flow diagram for recruitment of patients



For sample size estimation, the prevalence of anemia in children was taken as 59% (NFHS-4) [7]. At confidence interval of 95% and desired precision of 10%, the sample size was estimated to be 100. Detailed history (including sociodemographic profile and dietary history as per infant and young child feeding practices [8]), anthropometry (weight, height, mid upper arm circumference was taken, as per standard WHO guidelines, in children below 5 years of age only) and examination was done. Baseline investigations - CBC, peripheral blood smear (PBS), and reticulocyte count was sent in all the cases. Anemia was classified morphologically into microcytic, normocytic and macrocytic anemia, based on PBS findings.

Further laboratory workup included serum iron and ferritin, total iron binding capacity (TIBC) and transferrin saturation to identify iron deficiency anemia; serum vitamin B12 and folate for detecting megaloblastic anemia; both of the above for dimorphic anemia; hemoglobin electrophoresis to identify thalassemia and sickle cell anemia; total & indirect serum bilirubin, direct coomb's test, and screening for G6PD deficiency to rule out hemolytic anemia; bone marrow examination to exclude leukemia and aplastic anemia; ESR to determine anemia of chronic disease. Selection of a specific test amongst these, depended upon the history, examination and baseline investigations, which pointed out towards a specific cause of severe anemia. Other ancillary tests (urine and stool examination, ultrasonography, x-ray chest, serum widal, ELISA for HIV, gastric lavage for CBNAAT to rule out tuberculosis were done, whenever required.

Venous blood (about 2ml) was taken in ethylene diamine tetraacetic acid (EDTA) vial with aseptic precautions and sent for analysis to central laboratory (pathology department). CBC was performed by an automated hematology analyzer medonic M series M-32 system, which works on impedance and spectrophotometer principle. It estimates hemoglobin, hematocrit or Packed cell volume (PCV), RBC count, total leukocyte counts and platelet count. RBC indices - mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and red cell distribution width (RDW) were calculated from hemoglobin, hematocrit and RBC count. A peripheral blood smear was prepared (Leishman stain was used) and examined under microscope, to look for size, shape and different types of blood cells (microcytic /macrocytic /normocytic/ hypochromic/ normochromic /polychromasia /schistocytes /anisocytosis /poikilocytosis /ovalocytes/ pencil cells/tear drop cells/ hypersegmented neutrophils). Reticulocyte count was done by new methylene blue stain method, to differentiate between hypoproliferative and hemolytic anemia.

Serum iron and TIBC was quantitatively determined by ferrozine colorimetric assay. Serum ferritin level was determined by architect i method using chemiluminescent microparticle intrinsic factor assay. Serum vitamin B12 and folate was determined by architect method. The reference range for these hematological parameters vary with age [9]. Bone marrow aspiration was done from the iliac crest and smears were stained by Giemsa stain and examined under microscope.

Statistical analysis: The data was entered in Microsoft excel and biostatistically analyzed with SPSS software. Descriptive data, in terms of frequency and percentage was used for categorical variables and mean ± SD (standard deviation) for continuous variables. Chi- square test was used to assess the association of lower level of Hb with severe acute malnutrition (SAM). P-value<0.05 was considered to be significant.

Results

The mean age of severely anemic children was 37.59±31.43 months (age range 6 months-12 years). Males (56%) outnumbered females. The commonest age group was 6 to 24 months (46% cases), followed by 2–5-year age group (34%) and 5–12-year age group (20%). Prevalence of severe anemia (in admitted children) was found to be 1.8%. Half of the cases belonged to upper lower class of socioeconomic status and 58% belonged to joint family.

Sixty one percent of the mothers took antenatal iron for at least 100 days according

to the national guidelines. Most of the children were full term (77%), had birth weight between 1500-2500 gm (51%) and were fully immunized for age (67%). History of pica, worm infestation and blood transfusion in family members was found in 41%, 8% and 5% respectively. Amongst the feeding indicators, exclusive breast feeding till 6 months of age and continued breast feeding till 2 years of age was present in 56% and 43% children respectively.

Timely introduction of complementary feeding at 6 months of age, minimum dietary diversity and minimum meal frequency was found in 39%, 38% and 44% respectively. Only 35% of our children consumed iron rich foods whereas almost the same percentage of children were pure vegetarians. Anthropometry was done in 80 children only (age being 6 months to 5 years). The percentage of children who were underweight (WAZ score -2SD to -3SD) and severe underweight (WAZ <-3SD) were 32.5% and 18.75% respectively; stunting (HAZ -2SD to -3SD) and severe stunting (HAZ<-3SD) was present in 42.5% and 0% respectively; wasting (WHZ -2SD to -3SD) and severe wasting (WHZ<-3SD) was seen in 25% and 11% respectively. Moderate malnutrition (MUAC 11.5 - 12.5cm) and severe acute malnutrition (MUAC <11.5cm) was found in 31.23% and 25% cases respectively.

Fig-2: Distribution of cases according to predominant presenting complaint

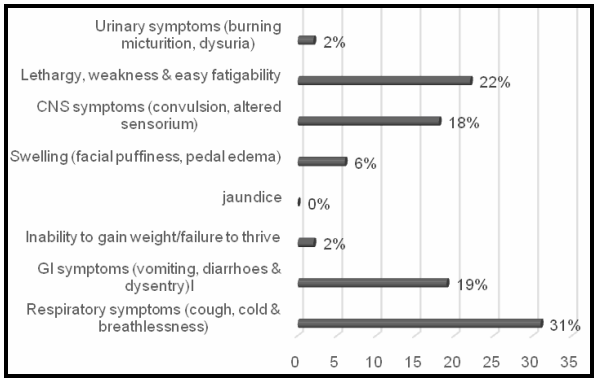


Figure-2 shows the common presenting complaints of the cases. At admission, respiratory symptoms were the commonest while none of the cases with severe anemia presented with jaundice. Frequency of children presenting with specific signs related to anemia, is shown in Table- 1.

Table-1: Percentage of children with specific signs related to severe anemia

	N	%
Signs of malnutrition (delayed milestone, failure to thrive, signs of vitamin deficiency, hair and skin changes)	25	25.0%
Hemolytic facies (Frontal bossing, malar prominence)	3	3.0%
Hyperpigmentation of knuckles	17	17.0%
Tremors	8	8.0%
Nail changes (koilonychias, platynychia)	0	.0%
Pallor	100	100.0%
Icterus	11	11.0%
Edema	34	34.0%
Lymphadenopathy	12	12.0%
Elevated body temperature	87	87%
Petechiae, purpura	12	12.0%
Hepatomegaly	63	63.0%
Splenomegaly	32	32.0%
Signs of congestive cardiac failure	36	36.0%

Pallor was the commonest sign found in all (100%) the cases, followed by elevated body temperature in 87% cases. Hemolytic facies was the least common sign found. Various hematological parameters are depicted in Table-2. Iron profile (serum iron, ferritin, TIBC and transferrin saturation) was done in 66 cases and serum vitamin B12 and folate was done in 33 cases as suggested by clinical presentation and baseline investigations.

Based on PBS, the most frequent morphologic type of anemia seen was microcytic hypochromic anemia (51% cases), followed by macrocytic anemia (20%), dimorphic anemia (17%) and normocytic normochromic anemia (12%). As regards etiology of severe anemia, iron deficiency was found to be the commonest cause in 45% cases, dimorphic anemia in 17% and megaloblastic anemia in 16% cases. Acute leukemia was seen in 7% children (6% had acute lymphoblastic and 1% had acute myeloblastic leukemia). Aplastic anemia was encountered in 4% cases. Beta thalassemia major, thalassemia trait and hereditary spherocytosis was found in 4%, 2% and 1% cases respectively.

Table-2: Various hematological parameters in study population						
	Mean	SD	Median	Percentile 25	Percentile 75	Valid in
Hemoglobin (gm/dl)	5.08	1.44	5.30	3.92	6.40	100
Total leukocyte count (cells /mm3)	17534	24475.37	14400	6600.00	18250.00	100
Platelets count (cells/mm3)	2.51	1.20	2.35	1.73	3.35	100
Total red blood cell count (million/mm3)	2.29	2.15	2.11	1.38	2.59	100
Red cell distribution width (%)	20.36	5.80	19.10	15.55	23.25	100
Mean corpuscular volume (femtolitres)	75.62	19.11	71.45	59.80	92.90	100
Mean corpuscular hemoglobin (picogram)	26.44	6.99	27.30	21.85	31.50	100
Mean corpuscular haemoglobin concentration (gm/dl)	34.64	4.48	34.95	31.85	37.40	100
Reticulocyte count (%)	.96	.59	.80	.60	1.20	100
Mean serum iron (µg/dl)	102.59	89.51	76.00	48.21	124.00	66
Mean serum ferritin (nanogram/ml)	332.13	315.01	214.00	50.00	484.00	66
Total iron binding capacity (µg/dl)	347.09	121.26	363.00	247.00	424.00	66
Transferrin saturation (%)	32.16	24.94	22.75	13.80	44.50	66
Serum vitamin B12 (picogram/ml)	381.66	462	186.00	132.00	386.00	33
Mean folic acid (nanogram/ml)	7.62	4.34	6.20	4.80	9.20	33

Out of total 80 children, aged 6 months to 5 years, SAM was present in 25 children. Of these 25 children having SAM, 16 children (64%) had relatively lower hemoglobin level of < 5 gm/dl as against 9 children (36%) who had hemoglobin level of 5-7 gm/dl. p - value was calculated to be 0.0138, which is considered to be significant. Table- 3 shows that SAM is associated with a relatively lower level of hemoglobin (Hb<5 gm/dl), in cases of severe anemia (defined as Hb < 7 gm/dl).

Table-3: Association of lower level of hemoglobin with SAM						
Variable	Hb <5 gm%		Hb 5-7gm%		Total	
	N	%	N	%	N	%
SAM (n=25, %)	16	64.0%	9	36.0%	25	100%
NON-SAM (n=55, %)	19	34.5%	36	65.5%	55	100%

Discussion

Prevalence of anemia in children is on rise, despite many government programs to prevent it. Anemia Mukt Bharat Strategy (which includes prophylactic iron and folic acid supplementation, deworming, delayed cord clamping, anemia testing and addressing non nutritional causes of anemia) has been implemented at all blocks, villages, districts and union territories [10].

Severe anemia is dangerous and often requires blood transfusion as a life saving measure. As per NFHS-5 data (2019-21), the prevalence of severe anemia, in children aged 6 -59 months, is 2.1%. Due to a broader exclusion criterion, wider age group (6 months -12 years) and study being conducted in admitted patients only, the prevalence of severe anemia (in admitted patients) of 1.8% was a bit lower in

our study (100 cases of severe anemia, out of total 5560 hospitalized patients, aged 6 months to 12 years). Study done by Ughasoro et al, Kubavat et al and kebede et al found prevalence of severe anemia to be 5.8%, 3.33% and 8.2% respectively in under 5 age hospitalized children [11-13].

Eighty percent of our severe anemia cases were observed in children under 5-year age, out of which about half (46%) were in the age group 6 months-2 years. The mean age of our study was 37.59 ± 31.43 months (age range 6 months -12 years), which was consistent with that of study done by Mendu et al (mean age was 3.94 years ±3.52, age range being 1 month-13 years) [14]. In the study done on hospitalized children, aged 6 months-12 years, Kokku et al [15] found that maximum number of severe anemia cases (39.6%) were in 6 months-2-year age group, similar to findings of our study (46% cases). The reason for higher frequency of severe anemia cases in younger children could be nutritional imbalance, as these children have higher nutritional needs due to rapid blood volume expansion and high rate of growth during the first two years of life. Also, the practices and timely initiation of complementary feeding is poor; breast milk is a poor source of iron and micronutrients; and higher susceptibility to infectious disease may affect absorption and utilization of micronutrients. Majority of our children (76%) belonged to low socioeconomic status, similar to the findings of study done by Kokku et al (77.3%) [15]. Rani et al reported higher prevalence of anemia in vegetarians and in low socioeconomic strata [16].

Fifty eight percent of our cases belonged to joint family; a finding similar to that reported by kokku et al in 56.4% cases [15]. Study done by Patel et al [17] on hospitalized infants showed that preterm gestation, absence of exclusive breast feeding, consumption of cow's milk, continued exclusive breast feeding beyond 6 months age and improper complimentary feeding practices were the risk factor associated with development of anemia, similar to our findings. History of worm infestation was found in 7.9% cases by Kokku et al [15], similar to our finding of 8%. Respiratory tract infection was the most common presenting complaint in our study, found in 31% cases, similar to the findings of study done by Janjale et al (age group 6-59 months) [18]. Elevated body temperature was found in majority (87%) of our cases. Similar finding was also reported by Kokku et al [15] and Jenifer et al [19] who found it in 76.2% and 64% cases respectively. Pallor was present in 100% cases in our study, similar to the findings of study done by Kukku et al [15] and Janjale et al [18].

Malnutrition (MUAC<12.5 cm) was seen in 45% of our cases, similar to that found by Janjale et al in 47% cases [18]. Microcytic hypochromic anemia was the most common morphological type (seen in 51% cases) in our study, similar to that found in study done by Vaswani et al (42% cases) [20] and Janjale et al (47.76% cases) [18]. Majority of our children (45%) were diagnosed to be having iron deficiency anemia, similar to the observation made by Janjale al [18] and Kokku et al [15].

Mean (SD) of Hb, MCV, MCH and MCHC was 5.08(1.44), 75.62(19.11), 26.44(6.99) and 34.64(4.48) respectively in our study; similar findings were observed by study done by Vaswani et al [20] who found them to be 5.22(1.39), 76, 20 and 26 respectively. SAM was found to be associated with lower Hb level of < 5 gm/dl in our study. Arya et al, in his study on SAM children (age group 6-59 months), reported that mean value of Hb was lower in children with SAM (7.17±2.26 gm/dl) as compared to non-SAM children (9.22±3.36 gm/dl) [21].

The limitation of this study was its cross-sectional nature, due to which establishing cause and effect relationship was not possible. Also, this study did not include modifiable risk factors e.g., CKD, CLD as well as common infectious diseases that potentially dysregulate hematopoiesis e.g., HIV, malaria, dengue etc. The study was conducted in admitted patients only, so it did not represent the prevalence of severe anemia in community.

Conclusion

Severe anemia is more common in under 5-year children. Early diagnosis of severe anemia with clinical and basal blood parameters, along with its etiology is essential

before start of treatment, to avoid unwanted side effects e.g., iron overload. Anemia is frequently associated with malnutrition, so there is a need for urgent community participation programs esp. counselling the parents for child feeding practices, apart from the ongoing deworming and iron-folic acid supplementation programs by the government.

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