VOLUME - 10, ISSUE - 02, FEBRUARY - 2021 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Paediatrics

CLINICAL AND EPIDEMIOLOGICAL PROFILE OF CHILDREN WITH MEGALOBLASTIC ANEMIA AT A TERTIARY CARE HOSPITAL IN WESTERN INDIA: A CROSS SECTIONAL STUDY

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ABSTRACT

Background: In India most cases of Megaloblastic anemia are caused by nutritional deficiency of vitamin B12 and Folic acid. Initial workup include Complete Blood Count(CBC), Peripheral blood smear(PBS) ,Vitamin B12 asssay, folic acid assay and Bone marrow if required. Therefore, this study is planned to study the clinical and laboratory profile of children with Megaloblastic anemia and to study the clinical outcome of children with Megaloblastic anemia

Methods: The study was a prospective observational study conducted among 60 children with megaloblastic anemia, aged 1-12 years. Demographic data, clinical symptoms and signs, laboratory findings, serum B12 and Folic acid ,Bone marrow report and stool routine microscopy report were collected. Chi square test was applied.

Results: Among the 60 children 40% were female sand 60% were males. The age of the study population ranged from a minimum of 1 month to a maximum of 12 years with a mean(SD) of 8.08 (± 5.45).Majority of children (41.6%) were in age group of 6 months- 1 year. Most common symptoms fever and most common sign is pallor. More than fifty percent cases presented with severe anemia. Many cases reported late, leading to delay in diagnosis leads to poor outcome. Developmental delay (neurological manifestation) is strongly associated with vitamin B 12 deficiency as compared to folic acid deficiency. (p value <0.05)

Conclusions: There is a slight female preponderance seen in megaloblastic anemia, probably due to reduced attention to girl children in the study group. neurological manifestation is strongly associated with vitamin B 12 deficiency as compared to folic acid deficiency.

KEYWORDS : Megaloblastic anemia, MCV, Vitamin B12

INTRODUCTION

Megaloblastic Anemia is defined as a form of macrocytic anemia which is characterized by a peculiar bone marrow morphological picture consisting of megaloblasts and metamyelocytes associated with thrombocytopenia and leukopenia.[1]This disease has a wide spectrum of clinical presentation from asymptomatic individuals to life-threatening myelopathy or pancytopenia. Identification and treatment of vitamin D deficieny is very essential as it is one of the reversible causes of bone marrow failure and nervous system disease.[2]

Nutritional deficiency had been postulated to be the main factor for the occurrence of this disease manifestations in a large population in India. Vegetarianism has been held responsible for causing megaloblastic anemia in several studies, both in India and in Asian communities who have migrated to western countries[3]. In India, most cases of Megaloblastic anemia are caused by nutritional deficiency of vitamin B12 and Folic acid and rarely due to inborn errors of metabolism (methylmalonic aciduria and methylene tetrahydrofolate reductase deficiency). Patients with megaloblastic anemia have symptoms of fever, loss of appetite, lethargy, numbness, tingling, tremor etc. and clinical signs of Megaloblastic anemia include hyperpigmentation of knuckles and terminal phalanges. Splenomegaly and Hepatomegaly is seen in up to 30-40% cases and hemorrhagic manifestations have been reported in upto 25% cases.[4] Initial workup for Megaloblastic anemia include Complete Blood Count(CBC), Peripheral blood smear(PBS) ,Vitamin B12 asssay, folic acid assay and Bone marrow if required. Macrocytosis is the earliest abnormality seen in complete blood counts of patients with folate or vitamin B12 deficiency.[5] Treatment depends on the underlying cause. Vitamin B12 deficiency is treated with intramuscular or oral vitamin B12 supplementation as 1000 microgram once daily for 10 days, followed by once a week for one month, and then after that once a month.[6]

OBJECTIVES

The objectives of the study are to study the clinical and laboratory profile of children with Megaloblastic anemia and to study the clinical outcome of children with Megaloblastic anemia

MATERIAL AND METHODS

Study design and setting:

The study was a prospective observational study conducted at the Department of Pediatrics and PICU (pediatric intensive care unit) of Urban Tertiary Care Teaching Hospital of Maharashtra state.

Study population :

The study population included children of age 1 month and 12 years with clinical diagnosis of megaloblastic anemia.

INCLUSION CRITERIA:

1. Age 1 month – 12 years
2. Child with clinical and/or laboratory diagnosis of megaloblastic anaemia.

EXCLUSION CRITERIA:

1. Children with other hematological conditions such as iron deficiency anemia, dimorphic picture, etc.,

2. Children with hematological malignancies.

STUDY DURATION: The study was conducted during from September 2018 to June 2019

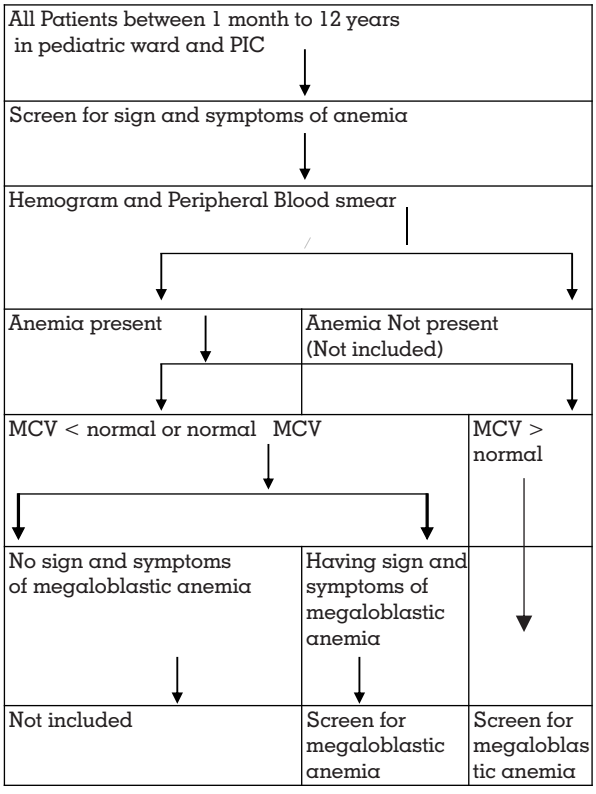
Sample size calculation :

The sample size for this study was calculated using the formula: $N=Z^2\times PQ/L2$, where, Z=1.96, N=sample size, p=assumed prevalence of Megaloblastic anemia in children, which was estimated prevalence taken as 5%, error (L) as 6% with a drop out rate of 10%, the calculated sample size was

Data collection procedure:

Consent from parents or guardians for the enrolment in the study was taken. All children had comprehensive physical, neurological and systemic examination at the time of admission. History, examination and sampling for hemogram, PBS(peripheral blood smear),serum B12,Folic acid was done soon after admission in every children. A standardized data entry form was used to document demographic data, clinical symptoms and signs, laboratory findings, serum B12 and Folic acid ,Bone marrow report(patients of whom Bone marrow has been done) and stool routine microscopy report of each patient at presentation. At our Institution, after collection sample sent to lab with in 1 hour in EDTA bulb and in plane bulbs. CBC(complete blood count)done by automated haematology cell counter. Vitamin B12 and Folic acid was done by electro chemiluminicence method. B12 and folic acid level of children with clinical suspicion of megaloblastic anemia are done for the confirmatory diagnosis. Mothers' hemogram were also done for megaloblastic anemia. Nutritional status of the child was assessed by WHO Classification. Anemia classification was done by WHO classification of anaemia. To decide MCV whether it was normal or more decided from DACIE book of Hematology.

Treatment- Intravenous vitamin B12 1000microgram daily for first week followed by weekly foe 1 to 2 months, and then monthly thereafter till vitamin B 12 get corrected.



Clinical outcomes :

The clinical outcomes of the diseases was recovery and death.

STATISTICAL ANALYSIS:

Data was analysed with Statistical Package for Social Sciences (SPSS IBM) version 21.0 software. Proportions and means were calculated. Tests of significance required was applied. A p value of <0.05 was considered statistically significant

Definitions :

1. **WHO NUTRITIONAL CLASSIFICATION**
2. Underweight : Weight for Age < -2 SD of WHO Child growth standard Median.
3. Stunting : height for Age < -2 SD of WHO Child Growth Standard Median
4. Wasting : Weight for Height < - 2 SD of WHO Child Growth Standard Median.
5. Overweight : Weight for Height > + 2 SD of WHO Child Growth Standard Median.

6. Severe Acute Malnutrition:-

a. Weight for height < -3 SD
b. Mid Arm Circumference < 11.5 cm
c. Nutritional oedema

7. Moderate Acute Malnutrition:- Weight for height <- 2SD to – 3 SD

- Mid Arm Circumference 11.5 cm to < 12.5 cm
- No oedema

2. **NORMAL MCV VALUES** (Mean ± 2 SD)

2 months : 95. ± 8
3 to 6 months : 78 ± 8
1 year : 78 ± 6
2 to 6 years : 81 ± 6
6 to 12 years : 86 ± 9

RESULTS

Among the 60 children 40% were female sand 60% were males. The age of the study population ranged from a minimum of 1 month to a maximum of 12 years with a mean(SD) of 8.08 (± 5.45).Majority of children (41.6%) were in age group of 6 months- 1 year, while 33.3 %were in age group of 1-2 years and 6.6% were in age group of > 2 years. (Table 1)

Table 1 Baseline characteristics of the study participants. (N=60)

S.No.	Variables	N(%)
1.	**Age group**	
	< 6 months	11(18.3)
	6 months - 1 year	25(41.6)
	1- 2 years	20(33.3)
	>2 years	4(6.6)
2.	**Sex**	
	Male	36(60)
	Female	24(40)
3.	**Diet**	
	Mixed	19(31.7)
	Vegeterian	41(68.3)
4.	**Nutritional status***	
	Severe acute malnutrition	28(46.6)
	Moderate acute malnutrition	14(23.3)
	Normal	18(36.7)

***WHO classification**

The most common symptoms amongst study population was fever(65%) followed by loss of appetite (61.7%), Irritability (58.33%) and Developmental Delay(46.66%).The most common signs amongst study population were pallor (100%) followed by Hyperpigmented Knuckle (78.3%), neurological manifestations (45%) and Hepatomegaly (43.33%) (Figure 1)

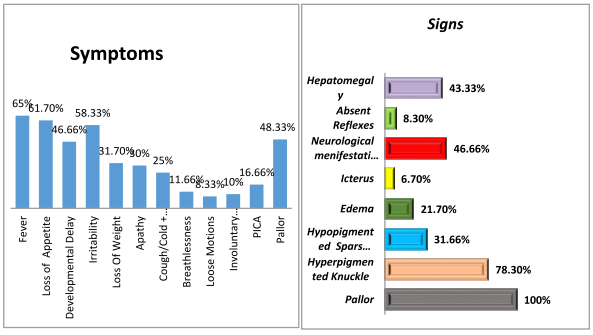


Figure 1 Symptoms and signs among the study participants. (N=60)

Table 2 Laboratory parameters of the study participants. (n=60)

S.No.	Lab values	N(%)
1.	**Hemoglobin (gm/dl)**	
	< 3	5(8.3)
	3 to 7	27(45)
	7 to 10	25(41.6)
	>10	3(5)
2.	**MCV**	
	<90	7(11.6)
	90-100	22(36.6)
	>100	31(51.6)
3.	**Cell count**	
	Pancytopenia	7(11.6)
	Bicytopenia	17(28.3)
	Normal blood smear	36(60)
4.	**Peripheral smear**	
	Macrocytic Hypochromic	21(35)
	Macro-Ovalocytes	24(40)
	Normocytic Normochromic	4(6.66)
	Hypersegmented Neutrophils	11(18.34)
5.	**Serum vitamin B12 and folic acid**	
	Low vitamin B_{12} level (<200pg/ml)	33(35)
	Low folic acid level (<3-7ng/ml)	10(16.6)
	Low vit. B_{12} and folic acid level	3(5)
	Normal Vitamin B12 and folic level	13(21.6)

Peripheral blood smear of macrocytic hypochromic, macro-ovalocytes,normocytic normochromic and hypersegmented neutrophils was present in 35%, 40%, 6.66% and 18.34% of study population respectively. Low serum level of Vitamin B-12, Folic Acid and both was present in 55%, 16.66% and 5%. 21.66% of study population had normal serum value.(Table 2)

Table 3 Diagnosis, treatment and outcome of megaloblastic anemia among the study participants.(n=60)

S.No.	Diagnosis, treatment and outcome of megaloblastic anemia	N(%)
1.	**Diagnosis**	
	Malnutrition with developmental delay	22(36.6)
	Malnutrition with infection	20(33.33)
	Infection with CCF	12(20)
	Developmental delay with ITS	6(10)
2.	**Treatment ***	
	Blood transfusion	12(20)
	Ventilation	5(8.33)
	Oxygen	17(28.33)
	Antibiotics	45(75)
	Injection B12	60(100)
	Folic acid	60(100)
3.	**Outcome**	
	Recovery	51(85)
	Death	2(3.3)
	Lost to follow up	7(11.66)

*Multiple options

All patients received Vit-B12 intravenously and folic acid also(100%) 75% ,28.33% cases required oxygen.(Table 3)

Table 4 Association between neurological manifestations and causes of megaloblastic anemia. (N=60)

Causes of megaloblastic anemia	Neurological manifestations		Total	P value
	Present	*Absent*		
B_{12} deficiency	25 (75.75%)	8 (24.25%)	33 (100%)	0.0078
Folic acid deficiency	3 (30%)	7 (70%)	10 (100%)	

Chi square test applied, p value < 0.05 is significant.

Statistical significant association was found between neurological manifestation ans Vitamin B12 deficiency. Chi square value (χ^2) =7.073, df (2),(p value-0.0078)

DISCUSSION

This was the cross-sectional observational study in which a total of 60 patients of megaloblastic anemia were studied. Out of 60 cases,41.66% belong to age group 6-12 months followed by 33.33% belongs to 1-2 year age group,18.33% belong to age group <6months,and6.6% belong to>2 years. Since, megaloblastic anemia is rare in the neonatal period so they were excluded from our study. Similar age group distribution and sex distribution was reported in previous studies.[7,8] Thus, slight female preponderance is noted among children with megaloblastic anemia.

In our study, out of 60 cases,65% children had fever which was most common symptom, followed by loss of appetite which were present in 61.7%, irritability 58.33%, paleness 48.33% and Developmental delay in 46.66%. In our study out of 60 children, 100% had pallor which is the most common sign followed by hyperpigmented knuckles in 78.3%,neurological manifestations in 45% and hepatomegaly in 43.3%.In a similar study by Nalli.R et al[8] pallor was the most common symptom found in 87.5% children, loss of appetite in 57.5%,weight loss in 45%,fever in 30% cases. In the study done by S.Srikanth et al[7] also, pallor is the most common sign noted in 95.2% cases, followed by wasting in61.9% , hepatomegaly in 81% and neurological signs in 33.3%.In the study by Nalli.R et al[8] 90% patients had hyperpigmentation of knuckle. Pallor is most common sign.

In our study, out of 60 cases,53.33% cases had severe anemia(<7gm%) ,41.66% had moderate anemia while 5% children had mild anemia. In a similar study by Nalli.R et al[8] 80% cases had moderate to severe anemia.In the study by S.Srikanth et al[7] 66.6% cases were had severe anemia. In our study out of 60 cases, MCV value of more than 100 in 51.66%,between 90-100 in 36.6% and less than 90 in 11.66% cases and average MCV value(89-114).

In our study, serum B12 level were done in all 60 patients and out of 60 patients 55% cases had low serum B12 level(<200 pg/ml), 16.66% children had low folic acid level(<3 ng/ml) as well and 5% patients had both. Out of 60 patients 13 (21.66%) had normal serum B12 and Folic acid level and in this group, bone marrow studies were done to arrive at the diagnosis of megaloblastic anemia. In a similar study by Nalli.R et al[75], 55% cases had low serum B12 and 12.5% had low folic acid level.. As our study included a majority of patients between the age group of 1 month to 1 year, B12 deficiency was the most common cause of megaloblastic anemia which is similar to the finding observed in similar studies discussed above. In our study, out of 60 cases bone marrow examination was done in 13 cases who had normal B12 and folic acid level. 76% out of 13 cases had megaloblastic change in bone marrow aspiration and 23.07% had normal bone marrow.

In our study, 8.33% required ventilation on admission because of associated comorbidities like pneumonia, out of which 3 cases recovered and 2 died.28.33% cases required oxygen supplementation by nasal canula.75% cases had received antibiotics as most of the patients presented with fever. All patients received intravenous B12 and folic acid after taking blood samples for serum B12 and folic acid, in view of suspected megaloblastic as early diagnosis and treatment can reduce neurological deterioration, complications and associated co-morbidities. Treatment of B12 and folate deficiency is cheap and affordable and timely administration is the key for management of megaloblastic anemia.Thus it could be concluded that along with iron and folic acid,B12 supplementation is needed through nutritional programmes.

Limitation

Our study has few limitations such as this was a hospital based study and generalizability to community findings is limited.

CONCLUSION

Megaloblastic anemia is most commonly seen in infants and young children with majority between 6 month- 2year. There is a slight female preponderance seen in megaloblastic anemia, probably due to reduced care to girl children in the study group. Most common symptoms fever and most common sign is pallor. More than fifty percent cases presented with severe anemia. Many cases reported late, leading to delay in diagnosis leads to poor outcome. Developmental delay (neurological manifestation) is strongly associated with vitamin B 12 deficiency as compared to folic acid deficiency.

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