RESEARCH

A STUDY OF CLINICAL SPECTRUM AND HEMATOLOGICAL PROFILE OF MEGALOBLASTIC ANEMIA AMONG CHILDREN IN A TERTIARY CARE CENTRE

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Received : 25/05/2022
Received in revised form : 03/08/2022
Accepted : 15/08/2022

Keywords:
Folic acid deficiency, Nutritional anemia, Pallor, Vitamin B12 deficiency.

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DOI: 10.47009/jamp.2022.4.4.2

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2022; 4 (4); 4-8

Abstract

Background: Megaloblastic anemia is one of the commonest causes of nutritional anemia next to iron deficiency anemia and is easily treatable. Megaloblastic anemia has a slow onset, the symptoms develop rather slowly, especially when compared to those of other types of anemia. It has varied clinical manifestations. The present study intends to describe the common presenting scenarios, and clinical and hematological manifestations of megaloblastic anemia in children admitted to a tertiary care hospital. **Materials and Methods:** It is a Hospital based cross-sectional observational study of 100 cases of megaloblastic anemia in children of age group 6 months to 12 years during the study period from November 2019 to November 2021 was conducted at Niloufer hospital. Clinical findings and hematological profile were obtained and statistical analysis of the data was done. **Result:** Of the 100 cases, 48% of them were in the age group of > 5 years, 46% were between 1- 5 years of age and 6% of them were less than one year of age and 53% of them were females and 47% of them were males. Of the 100 cases studied, fever was the commonest clinical presentation in 68% of the cases, easy fatigability in 38%, shortness of breath in 22%, vomiting in 15%, jaundice in 21%, and bleeding manifestations in 33%. On clinical examination, pallor was present in 100 % of the cases, jaundice in 21%, hepatomegaly in 84%, splenomegaly in 38%, signs of congestive cardiac failure (CCF) in 23 %, atrophic glossitis in 27%, and hyperpigmented knuckles in 30 %. **Conclusion:** The diagnosis of nutritional megaloblastic anemia should be considered when young children present with anemia in developing and underdeveloped countries.

INTRODUCTION

Nutritional anemia results when the dietary intake of nutrients is insufficient to meet the demands for the synthesis of hemoglobin and RBCs. The most common etiology is iron deficiency which contributes to almost 42% of cases in children under five years of age worldwide. However, this proportion of anemia due to iron deficiency varies depending on the age, sex, and the prevalence of other factors for anemia in that region. Deficiency of vitamins A, riboflavin (B2), pyridoxine (B6), cobalamin (B12), C, E, folic acid, and copper will also result in anemia.

Megaloblastic anemia usually results from a deficiency of either cobalamin (Vitamin B12) or folate, but may arise because of inherited or acquired abnormalities affecting the metabolism of DNA synthesis.

Nutritional megaloblastic anemia in children occurs commonly among under- nourished or malnourished societies of tropical and subtropical countries. The commonest age group affected is 3-18 months with a maximum number of cases being in 9-12 months.[1] These children are generally exclusively breastfed by mothers who are undernourished and have poor blood levels of folate and cobalamin.[2,3,4]

Folate deficiency is a more important cause of megaloblastic anemia and very little emphasis has been given to cobalamin deficiency. Over the last three decades, the prevalence of folate deficiency seems to have fallen from 70-75% to 2-10% as reported in various studies on children from different regions.[5,6,7] Hence cobalamin deficiency appears to be emerging as a significant contributor to nutritional

ISSN (O): 2687-5365; ISSN (P): 2753-6556

megaloblastic anemia. Diagnosing megaloblastic anemia assumes clinical importance as it responds well to the treatment.

According to the National Family Health Survey 5 (2019-2021), the prevalence of anemia (<11.0g/dl) among children of the age group 6-59 months is 67.5%.[8] The most common type of nutritional anemia is Iron deficiency anemia. Though folate and vitamin B12 deficiency also contributes to nutritional deficiency anemia, much emphasis is not laid on them. Hence the present study was taken up to know the various clinical features associated with megaloblastic anemia and correlate them with serum Vitamin B 12 and folic acid levels so that the etiology can be known, and therapy can be initiated early.

Megaloblastic anemia (MA) encompasses a heterogeneous group of anemias characterized by the presence of megaloblasts in the bone marrow.[9] This condition is due to impaired DNA synthesis, which inhibits nuclear division. Cytoplasmic maturation, mainly dependent on RNA and protein synthesis, is less impaired; this leads to an asynchronous maturation between the nucleus and cytoplasm of erythroblasts, explaining the large size of the megaloblasts.[10] This process affects the entire hematopoiesis as well as rapidly renewing tissues such as gastrointestinal cells. Megaloblastic anemia is most often due to hypovitaminosis, specifically vitamin B12 (cobalamin) and folate, which are necessary for the synthesis of DNA.[11]

MATERIALS AND METHODS

Place of Study

The study was done in the Department of Pediatrics, Niloufer hospital, affiliated with Osmania Medical College. It is the largest tertiary care center in the State of Telangana, situated in Hyderabad.

Study Design: Hospital-based prospective observational study

Study period: November 2019 - November 2021

Study Population: Children who were attending the outpatient department or who were admitted to Niloufer hospital with anemia during the study period.

Study Sample Size: 100

Methodology

Children who were admitted to Niloufer hospital with anemia with mean corpuscular volume >95fl, satisfying the inclusion criteria were enrolled in the study after getting informed consent from the parents/guardians.

Diagnosis of megaloblastic anemia was made by serum Vitamin B12 assay, serum Folic acid assay, or bone marrow examination.

Inclusion Criteria

i) Hemoglobin<11g/dl in the age group 6months-5yrs,
ii)Hemoglobin<10g/dl in the age group 5yrs-12yr
iii) Both genders iv) Children with the above-mentioned criteria whose parents/guardians gave informed consent.

Exclusion Criteria

i) Children of age <6 months and >12 years
ii) Children with hemoglobinopathies, aplastic anemia, and malignancies.
iii) Children whose parents/guardians have not given consent.

Children with anemia who fulfilled the inclusion criteria were admitted and enrolled in the study. A detailed history for every case enrolled in the study was taken from the parent/guardian. Physical examination was done, and significant findings were noted in the predesigned proforma.

Investigations such as i) complete blood picture ii) serum vitamin B12 and serum folate levels iii) bone marrow aspiration biopsy (wherever needed).

The treatment, investigations, and disease course were documented. The data was entered in Microsoft Excel 2010 version. Data were analyzed using Microsoft Excel 2010 and Epi Info 7.2.0. Descriptive and inferential statistical analyses were used in the present study. Results on continuous measurements were presented on Mean±SD (Min-Max) and results on categorical measurements were presented in Number (%). Significance was assessed at a 5% level of significance. Student t-test is used to compare inter-group variation for continuous variables. Pearson's Correlation Coefficient was used to assess the relationship between the two variables.

Ethical clearance was obtained from the Institutional Ethical Committee, Osmania Medical College, Hyderabad with ethical reference ID number-19101001009D. Vitamin B12 levels were also evaluated based on a published meta-analysis report which considers a value less than 148 pmol/L (200 pg/mL) as deficient. Normal serum vitamin B12 levels: 200-835pg/mL

Serum Folate levels: 5-20ng/mL. The deficiency was considered if levels were < 5ng/mL.

RESULTS

The study was done in the Department of Pediatrics, Niloufer hospital, affiliated with Osmania Medical College with an objective to study the clinical spectrum and hematological profile of children with megaloblastic anemia.

Among the study population, 46% (n=46) were between 1- 5 years, 48 % (n=48) in the age group of >5 years and 6% (n=6) of them were less than a year and 53 % (n=53) were females, followed by 47% (n=47) of males, shown in [Table 1].

Malnutrition was classified based on Waterlow's classification (wasting-low weight for height). It is classified into Normal (>90%), Grade 1(80-90%), grade 2(70-80%) and grade 3(<70%).

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Among the study population, 40% of them had normal weight according to Waterlow's Classification. 30% had Grade I malnutrition, 22% had Grade II malnutrition and 8% had grade III malnutrition. Dietary habits of these children showed that 19% were having a mixed diet and 81% were vegetarians.

Among the study population, 71% were lower middle class (11-15 score), and 29% were upper middle class (16-25 score) according to the modified Kuppuswamy classification of socioeconomic status.

In the present study, children with megaloblastic anemia presented with varied clinical presentation: fever was the presenting complaint in 68% of children, easy fatigability in 38%, shortness of breath in 22%, vomiting in 15%, jaundice in 21%, loss of appetite in 56 %, bleeding manifestations in 33% and other presenting complaints were cold, cough (30%), rash (6%), generalized swelling of the body (2%).

Clinical examination findings revealed pallor was present in 100 % of the cases, jaundice in 21%, hepatomegaly in 84%, splenomegaly in 38%, signs of congestive cardiac failure (CCF) in 23 %, atrophic glossitis in 27% and hyperpigmented knuckles in 30 % [Table 2].

Hematological profile of these children in the study showed, 27% of children had hemoglobin levels in between 6.1-7 gm/dl, whereas 22% had 5.1-6 gm/dl, 19% had 7.1-8 gm/dl, 18% had 4.1-5 gm/dl, 10% had 3.1-4 gm/dl, 3% had 8.1-9 gm/dl, 1% had 9.1-10; 58% of children had leucocyte count 4000-11000/cu.mm., whereas 28% had <4000/cu.mm., 14% had >11000/cu.mm.; 69% of children had Platelet count <1.5 lakhs/cu.mm., 20% had 1.5-4.0 lakhs/cu.mm., 7% had >4.0 lakhs/cu.mm. Peripheral blood smear findings of these children showed that 53% of the smears had anisocytosis, 62% had macrocytes, 29% had macro ovalocytes, 30% had microcytosis, and 15% had hypochromic cells. [Table 3] overall incidence of anemia, leucopenia, and thrombocytopenia in the present study.

Serum vitamin B12, and serum folate levels were measured in these children, 18% of the children were having serum vitamin B12 levels of <200 pg/mL (deficiency), 10 % of the children were having serum folate levels <5ng/mL (Deficiency), and 72% of the children were having combined vitamin B12 and folate deficiency.

Table 1: shows the age of presentation of megaloblastic anemia in our study.

Age group	Frequency	Percent
Less than 1 year	6	6%
1 – 5 years	46	46%
>5 years	48	48%
Total	100	100.00%
Mean ± Standard deviation	8.65 ± 3.16 years	
Range	7 months - 12 years	

Table 2: showing clinical examination findings in our study.

Examination findings	Frequency	Percent
Pallor	100	100%
Jaundice	21	21%
Signs of CCF	23	23%
Hepatomegaly	84	84%
Splenomegaly	38	38%
Atrophic glossitis	27	27%
Hyperpigmentation of knuckles	30	30%

Table 3: shows the incidence of anemia, leucopenia, and thrombocytopenia in the present study.

Finding	Frequency	Percentage
Anemia	100	100%
Leucopenia	28	28%
Thrombocytopenia	73	73%

DISCUSSION

Megaloblastic anemia is not rare, but the available data regarding its prevalence is insufficient. Nutritional megaloblastic anemia in children occurs commonly among under-nourished or malnourished low socio-economic societies of tropical and subtropical countries. The pathophysiology of anemia is ineffective erythropoiesis which results from abnormalities in DNA synthesis. Both vitamin B12 and folate deficiency may cause defective DNA synthesis, in which the nucleus and cytoplasm do not mature simultaneously. The cytoplasm (in which hemoglobin synthesis is unaltered) matures at the normal rate, and the nucleus (with DNA impairment) is not fully mature.

In the present study, 46% were in the age group of 1-5 years, and 48% were above the age group of >5 years. 6% belonged to the age group of less than a year. Similar findings were observed in a study done by Srikanth S. et al where, 66.6% were in the age group of 2 months – 3 years, 33% were in the age 13-15 years,[12] and in the study done by Phatake A et al,66.6% of the cases belonged to the age group of 6 months –3 years and 33% were in the age group of 10-12 years.[13] The increased incidence in the infant

ISSN (O): 2687-5365; ISSN (P): 2753-6556

age group can be attributed to improper weaning practices and continued exclusive breastfeeding due to the poor nutritional status of the mother and low levels of vitamin B12 and folate in the breast milk.

In the present study, 53% were females, and 47% were males. In a study done by Kumar A et al, females were 68% and males were 32%.[14] Our findings were consistent with the study done in western India, Sangli by Kene MK and Dhanawade S et al, females were 60% and males were 40%.[15]

In the present study, 71% belonged to lower-middle-class families according to modified Kuppuswamy classification and 19% were having mixed diet and 81% were vegetarians. Similar findings were observed in the study done by Kumar A et al where 80% of the study participants belonged to the lower class and 16% were having mixed diet, and 68% were vegetarians.[14] In a study done in Turkey by Mustafa Taskesen et al, 92% of the children belonged to low socio-economic families.[16] A study on megaloblastic anemia in children done in eastern Odisha showed that 57.33% of the children belonged to upper lower socioeconomic levels.[17,18,19]

In the present study, 68% presented with fever, 38% with fatigue, and 22% with shortness of breath (SOB), 15% with vomiting, 21% with jaundice, 56% with the loss of appetite, 33% with bleeding manifestations. The findings of the present study were comparable with the studies done on megaloblastic anemia as given in [Table 4].

In the present study, 100% had pallor, 23% had signs of congestive cardiac failure (CCF), 21% had Jaundice, 84% had hepatomegaly, 38% had Splenomegaly, 27% had atrophic glossitis, and 30% had hyper-pigmentation of knuckles. Hyperpigmentation results from decreased glutathione which induces tyrosinase activity, that in turn mobilizes melanocytes to keratinocytes, causing increased melanin synthesis.[20,21,22] The clinical examination findings of our study were comparable with similar studies as illustrated in [Table 5].

In the present study, anemia was present in all, followed by thrombocytopenia in 73%, and leucopenia in 28% of children. The incidence of anemia, thrombocytopenia, and leucopenia in various studies done on megaloblastic anemia is mentioned in [Table 6].

In the present study, Vitamin B12 deficiency was seen in 18% of cases, folic acid deficiency in 10% of cases, and combined deficiency was seen in 72% of cases. According to the study done by Reshmi Mishra et al., about 16.7% of the cases with megaloblastic anemia had Vitamin B12 deficiency and 9.3% of cases had a folic acid deficiency. Furthermore, 74% of the cases showed combined deficiency.[17] Our study findings were similar to studies done by Khanduri et al., and Chandra et al. where Vitamin B12 deficiency was more frequent than folate deficiency.[23,24]

This study from the region of the state of Telangana adds the findings to the existing literature. A large sample size would be preferable and reliable for drawing inferences. Furthermore, this study is a hospital-based one in a tertiary care center in Telangana, and patients seeking medical attention only were included. Hence, the actual burden of the children suffering from megaloblastic anemia may be the hidden part of an iceberg that should be explored with a suitable screening test that can be done at the community level. These facts should be taken into consideration in future studies.

CONCLUSION

Megaloblastic anemia can be of varied etiology and clinical presentation. The nutritional cause is most commonly due to folate deficiency and often the next common cause due to cobalamin - B12 deficiency is missed due to varied symptoms. As vitamin B12 deficiency can affect the nervous system and is associated with significant morbidity, an early diagnosis and management will go a long way towards a better quality of life. A simple modification in the dietary habits will prevent B12 deficiency which is associated with significant morbidity. As the present study is hospital-based, many undiagnosed cases in the community need to be identified and treated during contact with a health care professional.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556