

Study of Etiology and Varied Clinical Features of Megaloblastic Anemia in Adolescents at Niloufer Hospital

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Abstract:

Background: Megaloblastic anemia is becoming most common forms of anemia in adolescents during recent years. In India limited studies are available on megaloblastic anemia.

Objectives: To study the etiology by relative prevalence of vitamin B12 and folate deficiency and varied clinical presentations in adolescent with megaloblastic anemia.

Methods: Hospital-based cross-sectional observational study among 40 Adolescents (age 10-19 years) conducted in the Department of Pediatrics, institute for mother and child health (Niloufer hospital) Hyderabad, India during September 2013 to September 2014 with megaloblastic anemia in whom detailed history, relevant physical examination and anthropometry (height and weight) were recorded. Diet pattern of all the patients were noted. Cobalamin and folic acid assays were done.

Results: 70% were belongs to early adolescent age (10-14 yr). Significant proportion of patients were from middle and lower middle class (p value <0.05). 82.5% had vegetarian or a predominantly vegetarian diet pattern with a 95% confidence interval of 0.6722 to 0.9266. Most common symptoms were Pallor (87.5%) and fatigue (72.5%). The most common physical findings were hyper pigmented knuckles (90%) and Hyper pigmented distal phalanges (80%). Pancytopenia was found in 42.5% cases. 38 cases (95%) had either B12 or Folate deficiency.

Conclusion: Deficiency of either folate or B12 deficiency is common among the adolescents, which is common in vegetarian's diet patterns. Supplementation through implemented nutritional programmes and education regarding diet patterns may overcome this deficiency.

Key words: Adolescents, B12, folate, megaloblastic anemia.

I. Introduction

India is home to 243 million adolescents aged 10 to 19 years. Sadly, a large proportion of India's adolescents are anemic 56 per cent of girls and 30 per cent of boys. Anemia among adolescents adversely affects these young people's growth, resistance to infections, cognitive development and work productivity¹. It is the formative period of life when maximum amount of physical, psychological and behavioural changes take place². This is a vulnerable period in the human life cycle for the development of nutritional anaemia². At community level most cases of nutritional anaemia result from deficiency of iron. From public health viewpoint, deficiency of folate and B12 has been regarded to contribute little to nutritional anaemia. Megaloblastic anaemia (MA), in most instances in developing countries, results from deficiency of vitamin B12 or folic acid. Over the last two to three decades, incidence of MA seems to be increasing³ and is shown in several studies. A prospective study of profile of megaloblastic anaemia was done at a tertiary hospital in Uttarakhand was shown 48.8% were have megaloblastic anemia and In a study by Patra et al on severely anaemic adolescents admitted in a tertiary care hospital, megaloblastic anaemia was most common type of anaemia (42.5%) and iron deficiency accounted for 15% cases⁴.

II. Objectives

1. To study the etiology by relative prevalence of vitamin B12 and folate deficiency in adolescent patients with megaloblastic anemia at Niloufer hospital.
2. To study the varied clinical presentations of megaloblastic anemia.
3. To study the effect of megaloblastic anemia on the growth.

III. Methodology

The present study was a hospital-based cross-sectional observational study conducted in the Department of Pediatrics, institute for mother and child health (niloufer hospital) Hyderabad, India during september 2013 to September 2014. Adolescents (age 10-19 years) attending the outpatient department or admitted in the hospital, and having haemoglobin values <12 gm/dl in adolescents of 14 years of age; <13gm/dl in males 15

years and above and <12 gm/dl in non-pregnant females of 15 years and above (WHO criteria), MCV more than 95 fl and Bone marrow examination suggestive of a megaloblastic change in the marrow were included. Those who had received blood transfusion or haematinics in past (<6 months) or having apparent infection and any chronic diseases were excluded from the study.

All patients at the time of admission were taken up for Complete blood count using automated Sysmex blood cell counter with recording of MCV, MCH, RBC count, TLC and Platelet count. Those who qualified for inclusion criteria were taken up for bone marrow examination. Only those cases which were confirmed to have megaloblastic changes on bone marrow examination were included for final analysis. The common site for bone marrow aspiration in children is the posterior iliac crest and the medial aspect of the upper end of tibia just below the tibial tuberosity.

Cobalamin and folic acid assays were done by Chemiluminescence Immuno-Assay (CLIA method). Cases with serum cobalamin and folate levels of less than 200pg/ml and 5.0ng/ml respectively were considered as deficient^{5,6}. Iron studies were also done for the patients. The normal threshold in children is 12 μ g/dl. Values lower than this indicated Iron Deficiency Anaemia.

The patients were clinically evaluated in detail by history, relevant physical examination and laboratory investigations. Data was recorded in the proforma. Anthropometry (height and weight) was done for the cases included in the study and their growth pattern was evaluated as per CDC charts-2000. Statistical analysis was then done on the data and the study group was classified based on the z-scores for height for age and BMI for age. Socio-economic status was classified based on modified BG Prasad classification 2013⁷. Diet pattern of all the patients were noted and the patients were classified into three groups. Lactovegetarians were the patients who were not on any animal source diet for the last 5 years except for milk. Predominantly vegetarians were those who had a non-vegetarian (animal source) meal less than or equal to one time a month. Patients with mixed diet were those who regularly had animal source food like eggs, meat etc. along with the routine vegetarian diet. The severity of anemia was graded as mild (>10 g/dL but below age related cut-off for defining anemia), moderate (7-9.9 g/dL) and severe (<7 g/dL). Megaloblastic anaemia was diagnosed when the peripheral smear showed macrocytic anaemia with megaloblastic features, with MCV >95 fl.

Statistical Analysis and methods:

R Programming Software (Version 3.0.1) was used for Data Analysis. Descriptive statistics for Continuous variables were calculated as Mean and SD and for Categorical variables, frequencies were calculated. For Inferential Statistics, binomial and chi Square test was used. P value less than 0.05 was taken as significant.

IV. Observations and Results

Total of 48 patients had anemia, 8 Patients with recent (<6 months) history of blood transfusion and other serious co-morbidities were omitted from the study. The Mean age of patients with megaloblastic anemia was 13.2 years with a standard deviation of 2.05. Early adolescents were found to be more affective with 70% of the study group in the age group between 10 and 14 years. Out of the entire 40 patient's 17 patients (42.5%) were males and 23 patients (57.5%) were females. The statistical analysis by the binominal test showed the 95% confidence interval of 0.270429 to 0.591099 (P value = 0.4296). The females marginally outnumbered the males with male: female ratio of 1:1.35. This was found not to be significant upon analysis.

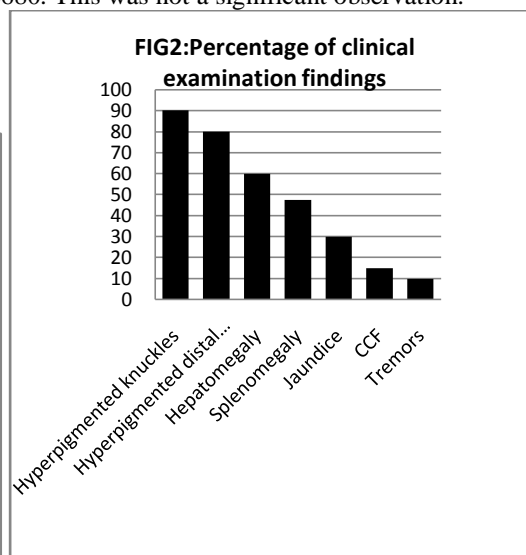
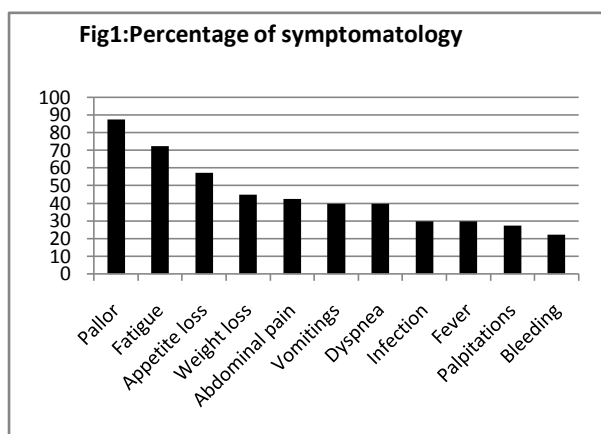
47.5% of the patients belonged to the class 3(c3) and 25% of the patients were from class 4 (c4). There were significant proportion of patients from middle class and lower middle class families (p value <0.05). Most of the patients were observed to be having vegetarian diet patterns with 67.5% patients being lacto-vegetarians. Another 15 % patients were those who consumed foods of animal origin very rarely (\leq once per month). The difference in diet pattern among the cases of megaloblastic anemia was quite significant with majority of the patients having a vegetarian diet pattern. (p value = <0.01). Patients with megaloblastic anemia were found to have a vegetarian or a predominantly vegetarian diet pattern with a 95% confidence interval of 0.6722 to 0.9266. More number of patients were from Hyderabad and Rangareddy districts (42.5%). The remaining cases were randomly noted to have been referred from the various districts of Andhra Pradesh without any demographic significance to any particular districts. The statistical analysis with Chi-squared test was not found to be significant with a p-value of 0.1425.

There was a high probability of cases to be from moderate and severe anemia group (80%) with a 95% confidence interval of 0.6435 to 0.9095. This was a significant observation with a p value of 0.00018. Pallor and fatigue were the most common and consistent clinical presentations among the patients. Pallor was found in 87.5% cases and fatigue was seen in 72.5% cases. Other common presentations included loss of appetite (57.5%), weight loss (45%), vomiting (40%) and dyspnea (40%). Fever, palpitations and bleeding was a clinical presentation in minority of cases (fig1).

Among the examination findings, the most common were hyper pigmented knuckles (90%) and Hyper pigmented distal phalanges (80%). Hepatomegaly was seen in 60% and splenomegaly was seen in 47.5 %,CCF was seen in 15 % cases and neurological manifestations like tremors were seen in a mere 10 % cases. Pancytopenia was a laboratory finding in 42 % cases of megaloblastic anemia. (fig2)

70% of the patients had a normal or above normal stature for age. BMI z-scores were done and 72.5% cases were normal and above with z-score >-2. These findings were not significant on statistical analysis.

38 cases (95%) had either B12 (82.5%) or Folate deficiency (40%). This was a significant finding as only 2 cases were found to have normal levels of B12 and folate. The 95% confidence interval was 0.8308 to 0.9938 and the p-value was <0.01. Either pure B12 (55%) or pure Folate (12.5%) deficiency were not found to be significant (p=0.6358). Combined deficiency was found in 11 cases (27.5%) with a 95% confidence interval of 0.1460 to 0.4388. Co-existing iron deficiency anemia (based on serum ferritin levels) was found in 5 cases (12.5%) with a 95% confidence interval of 0.0418 to 0.2680. This was not a significant observation.



V. Discussion

In India 70% under five children, 55% women and 24% men were anemic as per NFHS3 (2005-2006)⁸. Limited data is available on nutritional anemia in adolescents. As per previous studies from India iron deficiency was most common cause for anemia. But from the past two to three decades prevalence of folate and cobalamin deficiency is increasing and was shown in several studies. Both folate and B12 micronutrients deficiency causes megaloblastic anemia. It is commonly seen in infants with maternal B12 deficiency and adolescents. The present study mainly deals with megaloblastic anemia and the varied clinical presentations among the adolescent age group.

The study was a hospital based study on 40 adolescents with 1:1.35 male: female ratio. The females marginally outnumbered the males. The present study was in accordance with Khanduri et.al (2007)⁹ and Salma haq et.al (2012)¹⁰ with a female preponderance. A majority of the population (70%) was from early adolescent group. This might be ascertained to increased nutritional requirement in the pre-pubertal and pubertal ages which might put these children at risk for deficiency. The mean age of the study group was 13.2 years. This was similar to study done by EnverAtay et.al in 2014 from Turkey among adolescent population with megaloblastic anaemia had a mean age of 13.3 years¹¹. In a community based study conducted by Rajaratnam et al also noticed a decrease in prevalence of anaemia in adolescents in Tamil Nadu from 46.5% in 13-14yr age group to 42% in 17-19yrs age group, which was in contrast to study conducted by Biradar et al in Karnataka which showed a increasing prevalence of anaemia in adolescents with increasing age, with prevalence being 39% in early adolescence (10-14yrs) to 60% in late adolescence (15-19yrs)^{12,13}.

85% of study group belongs to lower 3 classes ie, 3, 4 and 5. Hence, this is a significant marker to megaloblastic anaemia being more prevalent among lower socioeconomic classes. This might be due to poor knowledge as well as affordability issue in this sector of population. 80% had moderate and severe anemia (p<0.05). Our study shows a high proportion of severely anaemic cases which can be attributed to hospital based nature of study which is in accordance with a similar hospital based study in children by Sandeep Ray¹⁴. 80% of cases were found to have a vegetarian or a predominantly vegetarian diet in the present study. Hence, a diet deficient in animal source is a significant cause of megaloblastic anemia (p-value = <0.01). This was compared to Khanduri et al 2007 in which 87% were vegetarians. Based on z scores, 72.5% of patients are normal (Z score>-3) and above the required BMI for age. Only 15% had moderate and 12.5% had severe wasting. This did

not have significance on statistical analysis. Micronutrient deficiency was common in malnourished individuals but our study patients had normal BMI probably due to small sample size. Malnutrition and anaemia are very closely related. In studies done by J Chandra et.al and A.Chhabra et.al, the incidence of PEM is 100% and 60% respectively¹⁵.

Pallor (87.5%) and fatigue (72.5%) were the most common clinical presentations. This was in accordance to Salma et.al (Lahore), A.Chhabra and many other studies. The second most common clinical presentation in this study was GI symptoms which was similar as A.Chhabra et.al¹⁶], whereas in Salma et.al dyspnea and palpitations were the second most common presentation followed by GI symptoms. Hyperpigmentation of knuckles and distal phalanges is the most common clinical findings seen in 80% and 90% of the patients respectively which is in accordance with J Chandra et al. Clinical finding on examination of these patients was hepatomegaly (60%) and splenomegaly (47.5%). The prevalence of hepatomegaly was in accordance to Chhabra et.al but the splenomegaly rates (47.5%) in the present study were almost twice that of Chhabra et.al (28.8%). The neurological findings such as tremors and parasthesias were low and found only in 4 patients (10%). This was consistent with J Chandra et.al and A Chhabra et.al who showed that these neurological manifestations to be 11.4% and 11.1% respectively, in their studies.

Pancytopenia was found in 42.5% cases with cells of all cell lines being affected mainly due to poor production. Thrombocytopenia is believed to be due to impaired DNA synthesis resulting in ineffective thrombopoiesis. This was consistent with Salma Haq et.al that showed a 41.3% cases with pancytopenia. Megaloblastic anemia can present with pancytopenia in many cases. This was shown in a pilot study of pancytopenia in adults done by R.S.Joshi et al. from MIMER medical college, Pune in 2010. Studies in the early sixties and seventies showed folate deficiency to be more common than vitamin B12 deficiency. This trend was seen both in developed as well as developing nations. Over the last few years, the cases of vitamin B12 deficiency are more commonly seen as compared to folic acid.

In the present study, vitamin B12(82.5%, $p<0.01$) deficiency was common than folate. In a study in Mexico on pre-school children, 41% had vitamin B12 deficiency while no case had folic acid deficiency. A study on adults and children from Zimbabwe showed three times more cases of vitamin B12 deficiency. Sarode et.al reported vitamin B12 deficiency in 74% cases compared to folate deficiency in 8.4% of megaloblastic anaemia. The present study was consistent with Khanduri et al, Chhabra et al and Chandra et al in the view that B12 deficiency was more common than folate. Co-existing iron deficiency was also documented. It was evaluated based on the ferritin levels. It was found in 12.5% cases which were not proved to be significant upon statistical analysis.

VI. Conclusion

We conclude that Megaloblastic anemia is common in an adolescent which is caused by deficiency of either folate or B12 deficiency. It has a significant correlation with diet pattern as it is more common in vegetarian people and predominantly is seen in low socioeconomic status. Pallor associated with hyper pigmented knuckles and hyper pigmented distal phalanges are most commonly associated with megaloblastic anemia. All cell lines of erythropoiesis are affected, resulting in pancytopenia. Along with iron and folic acid, B12 supplementation is needed through nutritional programmes. Periodic screening of adolescents may detect anemia at early stage and need for other supplements. Education about proper dietary habits is very essential. Large scale studies on the prevalence and etiology of Cobalamin deficiency in children and adolescents is needed as in recent years Cobalamin deficiency is increasing globally.

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