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Evaluation of Clinical Profile and Hematological Parameters of Cases of Megaloblastic Anemia

Hemang N Suthar[1], Tejas N Shah[2]

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Author's Affiliation:
[1]Associate Professor, Dept of Medicine, NHL Municipal Medical College, Ahmedabad; [2]Assistant Professor, Dept of Medicine, AMC-MET Medical College, Ahmedabad

Correspondence
Dr Tejas Shah
dr.tejasshah_333@yahoo.com

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ABSTRACT

Background: Megaloblastic anemia is not uncommon in India. In India, the most common cause of megaloblastic anemia is nutritional where as it is the pernicious anemia in Northern Europe.

Aims and objectives: To study age and gender-wise distribution, diet patterns, clinical features and hematological parameters in patients with megaloblastic anemia.

Material and methods: This was an observational cross-sectional study of the hundred patients of megaloblastic anemia. We included patients having anemia with MCV>100 fL, serum vitamin B12 level <250 pg/ml and/ or serum folic acid level<3 ng/ml with normal serum ferritin level were included. Detailed history, physical examination, laboratory parameters and radiological investigation were done.

Results: Megaloblastic anemia is most common in age between 20-40 years of age. Male subjects were commonly affected. Most of the patients (69%) belong to lower socio-economic class. 50% patients had severe anemia (Hb<7 gm %). Cobalamin deficiency was responsible for megaloblastic anemia in the majority of patients.

Conclusion: Megaloblastic anemia has wide clinical & hematological spectrum. The most common symptoms observed were a generalized weakness (98%), easy fatigability (96%), anorexia (64%) which is nonspecific, so high degree of suspicion is required to diagnose megaloblastic anemia.

Keywords: megaloblastic anemia, vitamin B12 deficiency

INTRODUCTION

Megaloblastic anemia is caused by impaired DNA synthesis due to deficiencies of vitamin B12 and/or folic acid which give rise to anemia and macro-ovalocytic red cells(MCV>100 fL) and bone marrow showing intense erythroid hyperplasia and megaloblastic changes[1]. Causes of megaloblastic anemia are vitamin B12 or folic acid deficiency or abnormalities of their metabolism[2]. Vitamin B12 is exclusively synthesized by bacteria and is found primarily in meat, eggs, milk and other dairy products[3]. The important cause of vitamin B12 deficiency is inadequate dietary intake due to pure vegetarian[4]. The main clinical features in more severe cases are those of anemia[5].Patient with cobalamin deficiency may complain of glossitis, angular cheilosis, vaginal atrophy, malabsorption, and diarrhea, or constipation[6]. The patient may have various neurological and neuropsychiatric features. There may be sub acute combined degeneration of spinal cord[7]. Leafy vegetables are principal sources of folic acid. The commonest cause of folate deficiency is nutritional[8]. Common symptoms of folate deficiency include diarrhea, macrocytic anemia with weakness, peripheral neuropathy, mental confusion, and forgetfulness or other cognitive declines, mental depression, swollen tongue, peptic or mouth ulcers, headache, palpitations, irritability, and behavioral disorders[6]. In megaloblastic anemia, there are macrocytes, ovalocyte and anisopoikilocytosis and hyper segmented neutro-

phils seen on pheripheral smear examination[9]. When anemia is severe, there is thrombocytopenia and pancytopenia[10].

Clinical features of megaloblastic anemia are varying from symptoms of severe anemia like weakness, fatigue, anorexia to neurological and neuropsychiatric manifestations. Typical signs and symptoms are frequently absent in early vitamin B12 deficiency[11]. Many symptomless patients are detected through finding of raised mean corpuscular volume (MCV) on routine blood count[5].Megaloblastic anemia leads to substantial morbidity if unrecognized or misdiagnosed[12]. Megloblastic anemia seems to be common in patients who present with symptomatic anemia in hospital in Gujarat due to vegetarian lifestyle. Very few studies have been conducted to study the prevalence of megaloblastic anemia in general population[1]. So we did a prospective study to document clinical features, hematological parameters, to determine which of two vitamins is a commonly responsible. We also looked for age and gender wise distribution and dietary pattern of the patients of megaloblastic anemia.

MATERIALS AND METHODS

We have studied 100 patients of megaloblastic anemia in a cross-sectional, observational study who are admitted to medicine wards or attending outpatients' medicine department, Smt. N.H.L. Municipal Medical College, Ahmedabad during period of October 2011 to November 2013.

In this study patients having anemia (Hb < 11 gm %) and MCV>100 fl with serum vitamin B12 level <250 pg/ml or/and serum folic acid<3 ng/ml with normal serum ferritin level included. Patients with age<15 years, on hematinics (past 6 months) or received blood transfusion are excluded from the study. Chief complaints of patients, detailed general and systemic examination and all investigation were performed. The complete neurological evaluation was done in all patients having neurological or neurocognitive complaints. Socio-economic status was classified based on modified BG Prasad classification 2013[11]. Diet patterns of all the patients were noted.

Complete blood count, RBC indices, examination of peripheral smear for cell morphology, renal and liver function tests, serum vitamin B12 level by ***chemiluminescence method***, serum folic acid level by ELISA and serum iron level were done in all patients. Cases with serum cobalamin and folate levels of less than 250pg/ml and 3.µ0g/ml respectively were considered as deficient. Serum TSH, free T3 and free T4 level were done in patients with symptoms of neuropathy and/or neurocognitive affection. Serum HIV was done in patients with symptoms of neuropathy or myelopathy. Few patients with symptoms of spinal cord involvement had undergone MRI screening of spine. The patients were clinically evaluated in detail by history, relevant physical examination and laboratory investigations.

OBSERVATION

In present study, out of 100 patients with megaloblastic anemia, there were 83 patients with only vitamin B12 deficiency, 10 patients with folic acid deficiency and 7 patients were with both deficiencies. 69(69%) of patients belong to lower socio economic class 30(30%) middle and 1(1%) belong to higher socio economic class. There were that 33(33%) addicted to alcohol and 13(13%) addicted to tobacco. 54(54%) patients were vegetarian (eating milk and dairy products) and 46 (46%) were taking mixed diet, among them 10(21.7%) patients had nonveg. food once in a week, 6(13%) had fortnightly, 30(65.2%) patients had occasionally and none of them takes daily, while none was vegan. Out of 54 vegetarian patients 46 patients were consuming milk and 8 patients were consuming milk products but not milk**.** Fatigue, anorexia, pallor, dyspnoea and paresthesia of limbs were most common presenting clinical features. In present study 34 patients had neurological features. Among them 31 patients had vitamin B12 deficiency, 2 patients had s. folic acid deficiency and 1 patient had both deficiencies. Among 31 patients with neurological features with pure vitamin B12 deficiency majority, 20(66.7%) were below 40 years.

Table 1: Demographic features of patients of megaloblastic anemia

Demographic features	Male (n=66)	Female (n=34)	Total (n=100)
Age group (Years)			
20-30	24(36)	12(35)	36(36)
30-40	23(35)	14(41)	37(37)
40-50	7(11)	3(9)	10(10)
50-60	7(11)	3(9)	10(10)
60-70	5(7)	2(6)	7(7)
Patients consuming milk in ml/day			
<250	8(40)	21(80)	29(63.1)
>250	12(60)	5(20)	17(36.9)
Hemoglobin level			
<7gm%	40(60)	10(29)	50(50)
7 to 9gm%	22(34)	06(18)	28(28)
>9gm%	04(06)	18(53)	22(22)
Different cell lineages			
Pancytopenia	40(60)	8(24)	48(48)
Anemia with leucopenia	4(6)	0	4(4)
Anemia with thrombocytopenia	7(11)	5(14)	12(12)
Isolated anemia	15(23)	21(62)	36(36)

Figure in parenthesis indicate percentage

Table 2: Megaloblastic anemia in different age group and severity of anemia

Hemoglobin (gm %)	Age group (years) (%)					Total (%) (n=100)
	20-30	30-40	40-50	50-60	60-70	
<7	22 (44)	22 (44)	2 (4)	2 (4)	2 (4)	50(50)
7 to 9	8 (28.6)	8 (28.6)	4 (14.3)	6 (21.4)	2 (7.1)	28(28)
>9	6 (27.3)	7 (31.8)	4 (18.2)	2 (9.1)	3 (13.6)	22(22)

Table 3: Comparison of hemoglobin values with serum vitamin B12 level

Hemoglobin (gm %)	serum vitamin B12 levels(pg/ml)				Total (n=83)
	50-100	100-150	150-200	200-250	
<7	18(36)	18(36)	12(24)	2(4)	50(60)
7to9	0	9(60)	6(40)	0	15(16)
9to11	2(11)	6(34)	10(55)	0	18(24)
Total	20(24)	33(40)	28(32)	2(4)	83(100)

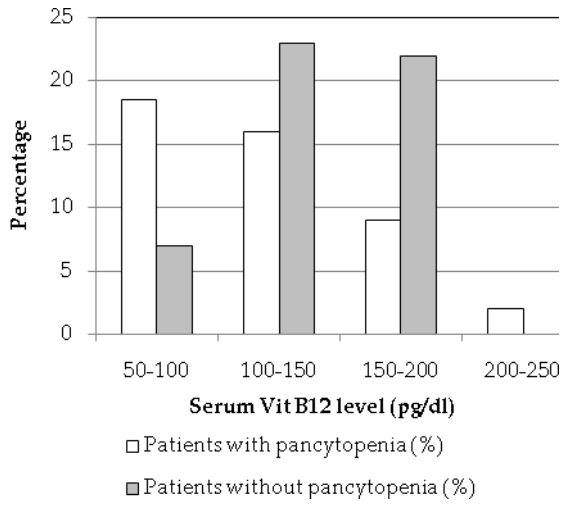

Chart 1: Comparison of patients with different white blood cell count with serum vitamin B12 levels

In present study, megaloblastic anemia with neurological features (n=34) found in form of neurocognitive affection with neuropathy 10(29%), myeloneuropathy 8(24%), neuropathy 7(21%), only neurocognitive affection 5(15%), myeloneuropathy with neurocognitive affection 2(5%) and cerebellar involvement with neuropathy 2(5%). In patients (n=34) presented with neurological features common symptoms were fatigue 34(100%), anorexia 20 (66.7%), headache20 (66.7%) psychiatric symptoms16 (53.36%), paraesthesias in upper limbs24 (47%), tingling of tongue 8(27%), ataxia 10(33.35%) and weakness in both lower limbs 10 (33.35%). In patients presented with neurocognitive involvement (n=17), all had depressive symptoms, headache and psychiatric symptoms like lack of concentration, irritability, lack of interest in a routine activity, mood disturbances, generalized body ache and sleep disturbances. In patients with neurological involvement(n=34), a majority of patients 22(64.7%) had hemoglobin more than 9 gm%, while only 12(35.2%) patients with hemoglobin less than 9 gm%, in which only 5(14.75) patients had hemoglobin below 7 gm%. Vitamin B12 level in patients with neurological involvement with pure vitamin b12 deficiency (n=31) was between 50-100 pg/ml in 4 (13.35%), between 100-150 pg/ml in 17(53.33%), between 150-200 pg/ml in 10(33.33%) patients.

When we have divided patients into three groups according to severity of anemia, 50 patients have hemoglobin less than 7 gm%. There were 28 patients with hemoglobin between 7 to 9 gm% and 22 patients with hemoglobin more than 9gm%.When patients were divided in to 2 groups on the basis of their serum vitamin B12 level (level<150pg/ml) and >150pg/ml but below 250 pg/ml, it was found that there was no significant difference between the mean hemoglobin of two groups ($p<0.05$ using independent t-test). There were 48 patients with pancytopenia and 60 patients were with thrombocytopenia. Patients with pancytopenia were almost equally distributed in various age groups divided according to s. vitamin B12 level. When patients were divided into two groups with and without pancytopenia; and serum vitamin B12 level < 150 pg/ml and no significant correlation between severity of vitamin B12 deficiency and presence of pancytopenia (chi-square test, P value 1.00).There were 62 patients having mean corpuscular volume (MCV) of 100-107 fl, 34 patients had MCV of 108-120fl.In 96% of patients, reticulocyte count is 2 or less than 2%. There were only 24(24%) of the patients had mild predominantly unconjugated hyperbillirubinemia. There were 86(86%) of the patients showed macro-ovalocyte, 16(16%) patients showed hyper segmented neutrophils. There were 10(10%) patients shows folic acid deficiency. Among them, 6(60%) patients with severe folic acid deficiency (< 1.5ng/ml) while 2(20%) patients with moderate folic acid deficiency and rest 2(20%) patients with mild deficiency (>2.5 but less than 3 ng/ml).There were 2 patients with serum folic acid deficiency and pancytopenia.

DISCUSSION

Pernicious anemia is the most common form of megaloblastic anemia in the West. In contrast, In India, pernicious anemia is uncommon[13]. Folate deficiency also causes megaloblastic anemia but recent studies suggested that vitamin B12 deficiency is also an important cause in India[12].

In present study, 73(73%) patients were below the age of 40 years and most common age of presentation of megaloblastic anemia was in subjects aged 20-30 years but all age groups were affected. As it affects all age groups so possibly related to inadequate diet. The most common age in another Indian study done by Khanduri and Sharma was in the age groups of 10-30 years[12]. The mean age of the patients of megaloblastic anemia was 33.83 ± 11.59 years which is comparable with study done by Andrew L in which it is below 50 years (76.5%) [14].There were 66 males and 34 females with male to female ratio approximately 2:1, which is comparable with study done by SR Kankonkar, in which it is 1.3:1[15]. In 34 patients having neurological manifestations out of which 21 were male and 13 were females with ratio 1.6:1. The male to female ratio was in severe anemia (n=50) and pancytopenia (n=48) cases 4:1 and 5:1 respectively.

There were 69(69%) patients from lower socio economic class which is comparable by study done by Singh R. in which it is 58%[16]. Patients belong to lower class were not afford milk, dairy products and balance diet. This is one of the important reasons for nutritional deficiency in our country[17].Out of 100 patients 54(54%) were vegetarian and 46(46%) were mixed vegetarian. Because the vitamin B12 does not occur in vegetable foods, vegans and strict vegetarian are at higher risk of developing megaloblastic Anemia[18]. In our study 46(46%) patients were having mixed diet, out of which large numbers of patients were taking occasionally non-vegetarian foods. There were no patients who were taking non vegetarian food daily. In our study there were 33% of patients who were chronic alcohol abusers. Consumption of alcohol is known to cause vitamin B12 and folic acid deficiency[18]. Chronic consumption of alcohol reduce folate store in liver, decrease absorption of folic acid and increase excretion of folic acid through urine.

Most common clinical features in our study were fatigue (96%), anorexia (64%); which is comparable with study done by SR Kankonkar et al in which it was 96.7% and 63.3%, respectively[15].Other common clinical features in our study were pallor (100%), dyspnoea (47%), paraesthesia of lower limbs (40%), skin pigmentation (32%), and paraesthesia of upper limbs (42%) ,nausea/vomiting(33%), headache(33%), glossitis and stomatitis (30%), edema (28%), psychiatric symptoms(30%), palpitation(16%), ataxia(17%), motor weakness in lower limb(15%),yellow discoloration of sclera and urine(12%),tingling of tongue(10%), weight loss(10%),diarrhea(2%) and bowel and bladder involvement(2%).In patients presented with neurological features common finding were weakness in lower limb(33.33%), absent ankle reflex(40%) and exaggerate knee reflex (33.77%) which is comparable with study done by J. Kalita et al in which it is 38.89%, 57.77% and 77.77% respectively[19]. Other findings in patient presented with neurological features were loss of joint position and vibration sensation (40%) and positive Romberg's test (40%).

In present study common hematological finding were pancytopenia (48%) which is comparable with study done by S. Apte in which it was36%[20].In megaloblastic anemia, there is ineffective hematopoiesis in all three cell lines with bone marrow hyperplasia and most of the precursor cells die within the hyper cellular marrow that's why pancytopenia is more common in Megaloblastic anemia[21]. Hyper segmented neutrophils were present in 22(22%) patients which is comparable with study done by J Kalita et al in which it is13.89%[19]. Macro ovalocyte was seen in 86 patients.

Among patients having neurological manifestation (n=34), severe anemia(Hb<7 gm%) was present only in 5(14.7%) patients, only 4(13.33%) patients were having pancytopenia and 22(64.7%) patients were having Hb more than 9 gm% and less than 11gm%. SR Kankonkar also noted that 39 patients with neurological involvement 87.72% had normal hemoglobin and only 12.28% had low values of hemoglobin[15].The neurological menifastions of vitamin B12 deficiency did not correlate with hemoglobin level. There were 8(8%) patients had type 2 diabetes mellitus and were on metformin for more than 5 years. Metformin reduce absorption of vitamin B12[22]. Another 2(2%) patients epilepsy and on tab. eptoin more than 5 years, showed severe folic acid deficiency.

CONCLUSION

We conclude by this study that megaloblastic anemia is more common in young adults with lower socioeconomically and male predominance, although all age groups are affected. Cobalamin deficiency was responsible for megaloblastic anemia in majority of patients and also in patients presented with neurological features. In majority patients presented with neurological features has mild anemia (Hb>9gm %) and vitamin b12 level moderately decreased (between 100-150pg/dl). Vitamin B12 deficiency must be considered in differential diagnosis of patients presented with chronic

neurological and neuropsychiatric symptoms. We propose vitamin B12 level should be first line test in all patients presented with anemia. The main limitation of the study is a single center observational study comprising a small sample size and so the results of the current study need to be confirmed in a multicenter study with large sample size.

REFERENCES

1. Sharma SK, Agrawal AK, Singal RK, et al. API textbook of Medicine, 10th edition. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd.; 2015. P 1268-73.
2. Snow CF. Laboratory diagnosis of vitamin B12 and folate deficiency: a guide for the primary care physician. Archives of internal medicine. 1999 Jun 28; 159(12):1289-98.
3. LeBlanc JG, Laiño JE, del Valle MJ, et al. B-group vitamin production by lactic acid bacteria–current knowledge and potential applications. Journal of Applied Microbiology. 2011 Dec 1; 111(6):1297-309.
4. Otten JJ, Hellwig JP, Meyers LD, editors. Dietary reference intakes: the essential guide to nutrient requirements. National Academies Press; 2006 Sep 12.
5. Kasper DL, Fausi AS, Hauser SL, et al. Harrison's textbook of internal medicine, 19th edition. New York: Mc Graw-Hill; 2015. P 640-9.
6. Braunwald E, Fausi AS, Kasper DL, et al. Harrison's textbook of internal medicine, 15th edition. New York: Mc Graw-Hill; 2001. p 674-80.
7. Healton EB, Savage DG, Brust JC, et al. Neurologic aspects of cobalamin deficiency. Medicine. 1991 Jul 1; 70(4):229-45.
8. Moll R, Davis B. Iron, vitamin B 12 and folate. Medicine. 2017 Mar 8.
9. Gupta M, Chandna A, Kumar S, et al. Clinicohematological profile of pancytopenia: A study from a tertiary care hospital Dicle Medical Journal 2016; 43(1): 5-11.
10. Gayathri BN, Rao KS. Pancytopenia: a clinico hematological study. Journal of laboratory physicians. 2011 Jan; 3(1):15.
11. Björkegren K, Svärdsudd K. Serum cobalamin, folate, methylmalonic acid and total homocysteine as vitamin B12 and folate tissue deficiency markers amongst elderly Swedes–a population-based study. Journal of internal medicine. 2001 May 14; 249(5):423-32.
12. Khanduri U, Sharma A. Megaloblastic anemia: prevalence and causative factors. National Medical Journal of India 2007; 20(4): 172-5
13. Desai HG, Anita FP. Vitamin B12 malabsorption due to intrinsic factor deficiency in Indian subjects. Blood 1972; 40(5):747-53.
14. Andrews L, Thomas T, Haridas N. Vitamin B12 status in tertiary care centre in central Gujarat. National Journal of community medicine 2012; 3(3):414-6.
15. Kankonkar SR, Joshi SV, Tijoriwala SJ, et al. A study of vitamin B12 deficiency of different diseases. Bombay Hospital Journal. 2004; 46.
16. Singh R. Socio-demographic factors causing anemia in adolescent girls in Meerut. Health & Population; Prospective and Issues 2008; 31 (3):198-203.
17. Jain T, Chopra H, Mohan Y, et al. Prevalence of anemia in relation to socio-demographic factors : cross-sectional study among adolescent boys in urban Meerut, India. Biology and medicine 2011; 3 (5): 1-05.
18. Allen LH. Causes of vitamin B12 and folate deficiency Food and nutrition bulletin. 2008 Jun, 29(2_suppl1): S20-34.
19. Kalita J, Misra UK. Vitamin B12 Deficiency neurological syndromes: correlation of clinical, MRI and cognitive evoked potential. Journal of neurology March 2008; 255(3): 353-9.
20. Apte S, Sinha U, Rajput V, et al. A study of various clinical features manifested due to the deficiency of vitamin B12 including detailed neurological and hematological feature. Journal of evaluation of Medical and Dental Sciences 2013; 2(47): 9184-9
21. Lee GR, Foerster J, Lukens J, et al. Wintrobe's Clinical Hematology, 10th edition. Baltimore: Lippincott Williams & Wilkins; 1999. 941-73
22. Kibirige D, Mwebaze R. Vitamin B12 deficiency among patients with diabetes mellitus: is routine screening and supplementation justified? Journal of Diabetes & Metabolic Disorders 2013 May 7;12(1):17