

Clinico-Haematological Profile of Megaloblastic Anaemia

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Abstract

Introduction: Megaloblastic anaemia is one of the important causes of anaemias. It is a macrocytic anaemia resulting from abnormal maturation of hematopoietic cells due to faulty DNA synthesis. Two vitamins, cyanocobalamin (vitamin B12) and folic acid are essential for DNA biosynthesis. Deficiency of either vitamin results in abnormal nuclear maturation with normal cytoplasmic maturation, apoptosis, ineffective erythropoiesis, intramedullary haemolysis, pancytopenia and typical morphological abnormalities in blood and marrow cells.

Methods: This descriptive study was carried out for two and a half years (July 2011 to December 2013) in the department of Pathology, Star hospital, Kathmandu, Nepal. Out of 885 anaemic patients 55 diagnosed as megaloblastic anaemia were included in the study. Complete blood count, reticulocyte count, peripheral smear and bone marrow examination were performed. Serum vitamin B12 and folic acid estimation was done in 32 cases.

Results: Out of 55 cases of megaloblastic anaemia, 31 were female and 24 were male with a female to male ratio of 1.3:1. Age range was 18 to 80 years. Pallor was the predominant clinical finding in these cases. Twenty cases (36.36%) presented with only anaemia while others presented with pancytopenia or bicytopenia. Of the 55 cases of megaloblastic anaemia, 32 had assays done for cobalamin and folate, of which 15 (46.88%) had cobalamin deficiency, 4 (12.5%) had folate deficiency and 13 (40.62%) had combined deficiency.

Conclusion: Megaloblastic anaemia can present with varied clinical manifestations. Strong suspicion of megaloblastic anaemia should be entertained by clinicians to improve clinical outcome. Prompt diagnosis is important as it is a completely curable condition.

Key words: Anaemia, Cobalamin and folate deficiency, Megaloblastic anaemia

Introduction

Anaemia is a major health problem worldwide. According to a recent World Health Organization report approximately 43% of the world's population is anaemic. Anaemia remains one of the most common and treatable morbidities suffered by individuals in developing world.

The etiology of anaemia is multi-factorial involving different factors including nutritional deficiencies, genetic red blood cells disorders and infectious disorders.^{1,2,3}

Megaloblastic anaemia is one of the important causes of anaemias. It is a macrocytic anaemia resulting from abnormal

maturation of hematopoietic cells due to faulty DNA synthesis. Two vitamins, cyanocobalamin (vitamin B12) and folic acid are essential for DNA biosynthesis. Deficiency of either vitamin results in abnormal nuclear maturation with normal cytoplasmic maturation, apoptosis, ineffective erythropoiesis, intramedullary haemolysis, pancytopenia and typical morphological abnormalities in blood and marrow cells.^{4,5,6}

Diagnosis of megaloblastic anaemia requires complete blood count, peripheral smear and bone marrow aspiration. Cytopenias e.g. bicytopenia and pancytopenia are common findings. Megaloblasts, giant metamyelocytes and bands are present in the bone marrow. Ineffective erythropoiesis and premature death of cells decreases the output of cells from the bone marrow, hence anaemia occurs.

The aim of this study was to evaluate the varying clinico-haematological manifestations in patients diagnosed as megaloblastic anaemia, attending Star hospital in Kathmandu, Nepal.

Methods

This descriptive study was carried out for two and a half years (July 2011 to December 2013) in the department of Pathology, Star hospital, Kathmandu, Nepal.

Out of 885 anaemic patients 55 diagnosed as megaloblastic anaemia were included in the study. The inclusion criteria for the study were haemoglobin level <10gm/dl and mean corpuscular volume (MCV) > 100fl. Macrocytosis in peripheral smear and hypercellular marrow with megaloblasts, giant metamyelocytes on bone marrow examination.

Complete blood count, reticulocyte count, peripheral smear and bone marrow examination were performed. Serum vitamin B12 and folic acid estimation by Chemiluminescent microparticle immunoassay (CMIA) was done in 32 cases. Complete blood count was done using cell counter Nihonkohden. Peripheral smear was stained by Leishman stain and evaluated for red cell morphology, white cell morphology and platelet count. Reticulocyte count was done by using 1% Brilliant Cresyl blue stain. Bone marrow aspiration was performed by Salah needle from posterior superior iliac spine. The slides were stained by Giemsa stain. Data was analyzed using SPSS 16.0 and Microsoft word and Microsoft Excel have been used to generate graphs and tables.

Results

Out of 55 cases of megaloblastic anaemia, 31 were female and 24 were male with a female to male ratio of 1.3:1. Age ranged from 18 to 80 years. (Table 1)

Table 1: Age and sex distribution of megaloblastic anaemia

Age groups	Male	Female	Total
<20 years	2 (9.52%)	3 (8.82%)	5 (9.09%)
20-40 years	5 (23.81%)	7 (20.59%)	12 (21.82%)
41-60 years	8 (38.1%)	16 (47.06%)	24 (43.64%)
>60 years	6 (28.57%)	8 (23.53%)	14 (25.45%)
Total	21 (38.18)	34 (61.82%)	55 (100%)

Clinical findings of patients with megaloblastic anaemia are listed in **Table 2**. Pallor was the predominant clinical finding in these cases. These patients mainly presented with generalized weakness, fatigue, palpitations, dyspnea and gastritis. Eleven patients (20%) presented with bleeding manifestations. The bleeding was mainly seen in skin and subcutaneous tissue.

Table 2: Clinical findings of patients with megaloblastic anaemia

Clinical findings	No. of cases	Percentage
Pallor	20	36.36%
Pallor+fever	11	20%
Pallor+bleeding manifestations	11	20%
Pallor+splenomegaly	08	14.55%
Pallor+splenomegaly+bleeding manifestations	05	9.09%
Total	55	100%

Cytopenias are a common manifestation of megaloblastic anaemia. Twenty cases (36.36%) presented with only anaemia and others presented with pancytopenia and bicytopenia. (**Table 3**)

Table 3: Cytopenias in megaloblastic anaemia

Cytopenias	Cases (%)
Anaemia	20 (36.36%)
Anaemia + leucopenia	03 (5.45%)
Anaemia + thrombocytopenia	10 (18.19%)
Anaemia + thrombocytopenia + leucopenia	22 (40%)
Total	55 (100%)

Reticulocyte count was found to be $>2\%$ in 31 cases (56.36%). The peripheral smear of these cases predominantly showed macrocytes and macrovalocytes (Figure 1). Substantial number of tear drop cells, leucopenia and thrombocytopenia were also observed. Hypersegmented neutrophils (>5 lobes) was present in all peripheral blood smears and ranged from 2% to 15% of neutrophils.

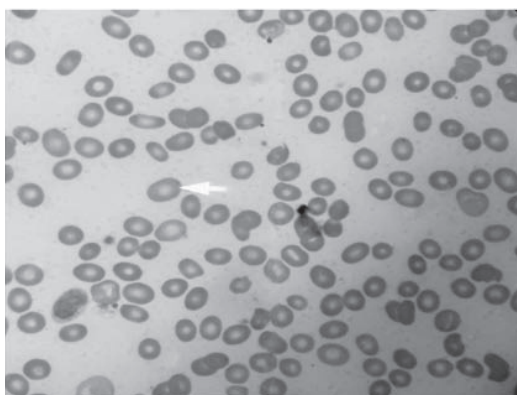


Figure 1: Peripheral blood smear showing macrovalocyte (Leishman stain, X1000)

Bone marrow smears were hypercellular with megaloblasts (Figure 2) in erythroid series and myeloid series of cells showed giant metamyelocytes and large band cells.

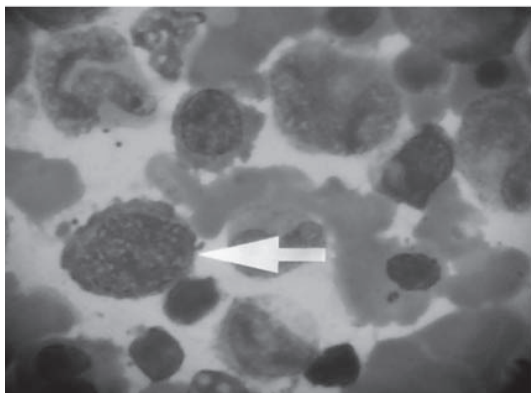


Figure 2: Bone marrow aspiration smear showing megaloblast (Giemsa stain, X1000)

Of the 55 cases of megaloblastic anaemia, 32 had assays done for cobalamin and folate, of these 15 (46.88%) had cobalamin deficiency, 4 (12.5%) had folate deficiency and 13 (40.62%) had combined deficiency (Figure 3).

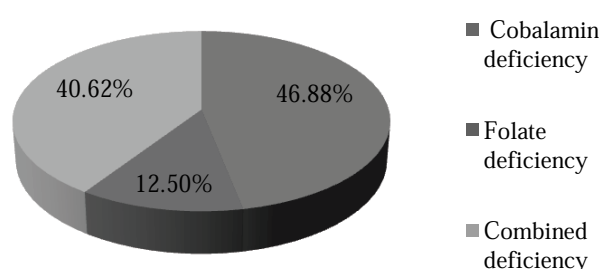


Figure 3: Distribution of 32 cases according to cobalamin and folate deficiency

Discussion

Megaloblastic anaemia is an anaemia that results from inhibition of DNA synthesis in red blood cell production. When DNA synthesis is impaired, the cell cycle cannot progress from the growth stage to mitosis stage. This leads to continuing cell growth without division, which causes nuclear-cytoplasmic asynchrony and presents as macrocytosis. The defect in red cell DNA synthesis is most often due to hypovitaminosis, specifically a deficiency of cobalamin or folate or both. Megaloblastic anaemia is a distinct type of anaemia characterized by macrocytic red blood cells and typical morphological changes in RBC precursors.^{7,8}

The common age of presentation of megaloblastic anaemia in our centre was between the ages of 41–60 years (43.64%) with female (61.82%) preponderance. In other studies megaloblastic anaemia is reported to occur in older age groups with an equal sex ratio or male preponderance.^{9,10,11} The prevalence of cobalamin and folate deficiency is seen with increased age due to low cobalamin and folate or metabolically significant increased cobalamin and folate deficiency. In our context megaloblastic anaemia was more common in females (61.82%) because they tend to be vegetarian due to the religious and cultural practices of our country.

Clinical examination of patients in our study showed pallor in all 55 cases (100%). Other studies found 98.8% to 100% patients presenting with pallor.^{12,13,14} Fever was seen in 20% of patients in our study, the commonest cause being infection to which the individual is much more susceptible in this disease due to impaired intracellular killing of ingested bacteria by neutrophils and macrophages.^{15,16,17,18} Bleeding was noted in 20% of patients in our study, it could be most likely due to thrombocytopenia. An earlier series documented bleeding in 17% to 20% of patients in megaloblastic anaemia.^{8,15,16} Haemorrhagic emergencies like intracranial bleeding and gut bleeding though not well appreciated in this disease have been rarely seen.

In our study pancytopenia was seen in 40% of patients. Similar findings (43% to 72%) have been reported by other authors.^{13,19,20} Thrombocytopenia was seen in 18.19% of patients. In other studies it has been ranged from 9.9% to 37%.^{8,18,20,21} Thrombocytopenia is believed to be due to impaired DNA synthesis resulting in ineffective thrombopoiesis. Megaloblastic anaemia is an important cause of cytopenias. It is generally believed that as severity of anaemia increases, thrombocytopenia develops followed by leucopenia and pancytopenia.

Out of 32 cases in which serum levels of cobalamin and folate levels were estimated, 46.88% cases clearly revealed predominance of cobalamin deficiency. Over the last four decades, the proportion of cases having cobalamin deficiency appears to have increased. This increase in cobalamin deficiency appears to be a global phenomenon as recent reports appearing from other developing countries indicate. A Zimbabwean study on megaloblastic anaemia reported cobalamin deficiency being three times more common than folate deficiency.²²

The average Nepalese vegetarian diet is deficient in cobalamin. It is possible that the increased demand during different age group in a population already deficient in cobalamin precipitates the anaemia.

A complete blood count with red cell indices, examination of peripheral blood smear, bone marrow aspiration and assay of the two vitamins are sufficient to make a definitive diagnosis of megaloblastic anaemia.

Conclusion

Megaloblastic anaemia can present with varied clinical manifestations. Strong suspicion of megaloblastic anaemia should be entertained by clinicians to improve clinical outcome. Prompt diagnosis is important as megaloblastic anaemia is a completely curable condition. Long term follow up and diet counseling should be done. The fortification of diet to prevent megaloblastic anaemia needs to be taken up as a national public health issue.

Conflict of interest: None declared.

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