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EVALUATION OF MACROCYTOSIS IN PATIENTS OF BIHAR

Pathology

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ABSTRACT

INTRODUCTION- Macrocytosis is a relatively common finding in routine CBC and peripheral blood smear. It is divided into two groups– megaloblastic and non-megaloblastic groups based on morphological and biochemical findings.

MATERIALS AND METHODS- We conducted this study in the department of pathology, Nalanda medical college, Patna, Bihar over a period of 18 months (September 2018 to March 2020). Sixty adult patients (>18 years) with macrocytosis (MCV>100fl) were evaluated in our study. Various tests were done to establish the cause of macrocytosis.

RESULT – The most common cause of macrocytosis was megaloblastic anemia due to vitamin B_{12} deficiency (53.3%). Non-megaloblastic anemia was caused by liver disorder (18.33%) followed by primary bone marrow disorders (10%).

CONCLUSION- The commonest cause of macrocytosis is megaloblastic anemia, but there are multiple non-megaloblastic causes with different mechanism and different treatment approach. Early detection of macrocytosis and its etiology helps in proper management of the patient with better outcome.

KEYWORDS

macrocytosis, megaloblastic anemia, non-megaloblastic anemia

INTRODUCTION

Erythrocytes are classified into three morphological groups by their mean cell volume (MCV): microcytic, normocytic, and macrocytic. Macrocytosis is the enlargement of erythrocytes more than 2 standard deviations than the normal value of the age group. The normal adult MCV ranges from 80-100 femtolitres (fl). MCV more than 100 fl is indicative of macrocytosis. Macrocytosis can be identified by reviewing peripheral blood smears and/or by automated RBC indices. The peripheral blood smear examination is more sensitive in identifying macrocytosis especially in early stage of diseases when there are small numbers of macrocytes in the circulation. The reported prevalence across various studies range from 1.7-4% [1,2]. MCV is calculated using following formula-

MCV (fl) = [Hematocrit (percent) x 10]/[RBC count (10^6/μL)]

Macrocytosis can occur physiologically in newborns, infants and pregnant women. Spurious macrocytosis is seen in multiple myeloma, hyperglycemia and in the presence of cold agglutinins [3,4]. Reticulocytosis also causes falsely high MCV. In some instances macrocytosis without anemia is seen in family members, which suggests a genetic predisposition, and requires no therapeutic intervention or further investigation [5,6].

The causes of macrocytosis can be broadly classified as megaloblastic and nonmegaloblastic depending upon the underlying pathogenesis and bone marrow findings. Megaloblastic processes are characterized on the peripheral smear by macro-ovalocytes and hypersegmented neutrophils, which are absent in nonmegaloblastic macrocytic processes. Nonmegaloblastic processes have round macrocytes or macroreticulocytes.

The most common cause of megaloblastic anemia is vitamin B_{12} deficiency followed by folic acid deficiency. The deficiency of vitamin B_{12} and folic acid causes delayed nuclear maturation and defective cellular division leading to very large size of erythrocyte precursors. Bone marrow is hypercellular and WBC and platelets are also affected. Presence of hypersegmented neutrophil is a relatively specific feature of megaloblastic anemia. Nonmegaloblastic processes develop from multiple mechanisms. Macrocytosis can occur when there is increased RBC production secondary to peripheral blood cell destruction (hemolysis) or loss (hemorrhage), leading to a reticulocytosis. Liver disorders cause macrocytosis by multiple mechanisms including defective cholesterol esterification causing excess lipid in RBC membrane, secondly by decreased storage of vitamin B_{12} and folate in advanced liver disease and third mechanism is by inducing haemolytic anemia in late cases of liver disease thereby causing reticulocytosis [8,9].

We conducted this study to evaluate the causes of macrocytosis and their associated haematological features.

MATERIAL AND METHODS

This study was conducted from September 2018 to March 2020 in the department of Pathology, Nalanda medical college, Patna. We evaluated 60 adult patients (>18 years age) with macrocytosis during this period. Presence or absence of anemia was noted. Anemia was defined as haemoglobin level < 13gm/dl in males and < 12 gm/dl in females. Pregnant women were excluded. Patients with reticulocytosis, spurious macrocytosis and where cause of macrocytosis could not be identified were also excluded from the study.

Thorough clinical history including family history, drug history, dietary history, addiction to alcohol and any past illness or surgery were noted and physical examination done.

All the patients were first evaluated by complete blood count and peripheral blood smear. Based on the positive findings from clinical history and physical examination other relevant tests were done which included serum vitamin B_{12} level, serum folic acid level, liver function test, renal function test, thyroid hormonal assay, blood sugar, bone marrow aspiration and biopsy. Vitamin B_{12} and folic acid deficiency were defined as serum cobalamin level < 203 pg/ml (or <150pmol/l) and serum folate level < 4ng/ml (or <10 nmol/l) respectively.

Table 1: causes of macrocytosis

Sl. No.	Etiology	Cases	Percentage
1.	Vit B_{12} deficiency	32	53.3%
2.	Combined vit B_{12} & folate deficiency	5	8.33%
3.	Liver disorder	11	18.33%
4.	Aplastic anemia	3	5%
5.	Myelodysplastic syndrome	1	1.67%
6.	Drug related	3	5%
7.	Hypothyroidism	2	3.33%
8.	Acute leukemia	2	3.33%
9.	Chronic renal failure	1	1.67%
	Total	60	100%

Table 2: Hematological profile of patients in two groups [mean and range]

Indices/ features	Megaloblastic group {n=37}	Non-megaloblastic group {n=23}
Hb (g/dl)	6.8 (3.0-11.8)	7.9 (4.2- 12.0)

RBC count (x 10^{12}/ lit)	2.4 (0.6-4.8)	3.18 (0.9-5.1)
MCV (fl)	116 (103-146)	106 (101- 114)
MCH (pg)	35 (28-45)	33 (31-44)
WBC count (x 10^9/l)	5.5 (1.4- 11.8)	6.6 (3.5-19.9)
Platelets count (x10^9/l)	155 (23-644)	290 (110-712)
Serum LDH (units/l)	1250 (880-1850)	280 (75-400)
Serum vit B_{12} level (pg/ml)	126 (30-150)	Not done in all cases
Hypersegmented neutrophils	86.5%	9%

RESULT

Total 60 patients with macrocytosis were evaluated in our study. There were 40 males out of which 32 were Hindu and 8 were Muslim, & 20 females out of which 17 were Hindu and 3 were Muslim. Hemoglobin level varied from 3.0 gm/dl to 12.0 gm/dl. Megaloblastic anemia was seen in 37 patients i.e. 61.67% (table 1). Isolated vitamin B_{12} deficiency was seen in 32 patients and combined vitamin B_{12} and folate deficiency was seen in 5 patients. Liver disorders were the second commonest cause of macrocytosis and the most common cause of non-megaloblastic anemia, accounting for 11 cases (i.e. 18.33%).

Hemoglobin level was lower in megaloblastic group in comparison to non-megaloblastic group (table 2). RBC count was lower and MCH, MCHC & serum LDH level were higher in megaloblastic group in comparison to non-megaloblastic group.

Bone marrow examination was done in 12 patients who showed aplastic anemia in 3 cases, acute leukemia in 2 cases, myelodysplasia in 1 case and megaloblastic anemia in rest 6 patients. Drug related macrocytosis was seen in 3 cases in our study. The offending drugs were valproic acid, metformin and zidovudine each in one case. Hypothyroidism was seen in 2 patients and CRF in one patient.

DISCUSSION

The etiology of macrocytosis differs in different populations depending upon dietary habits, alcoholism, prevalence of other diseases (e.g. autoimmune gastritis, autoimmune thyroiditis, HIV etc and related drug therapy) and structure of population (i.e. younger / older age group with increasing incidence of malignant hematological disorders in older age group patients). For example, in New York, 37% of cases diagnosed in hospitalized patients were medication related [10]. Antiretroviral therapy (ART) for human immunodeficiency virus (HIV) infections accounted for 13%. In Finland, the common causes of macrocytic anemias were alcoholism (65%) [11] and vitamin B12 or folate deficiency (28%) [12] in outpatients over 75 years of age.

Vitamin B_{12} deficiency was the commonest cause of macrocytosis in our study followed by liver disorders and primary bone marrow disorders. Our result correlates with that of McPhedran et al [13] and Unnikrishnan V [14]. Vitamin B_{12} deficiency is common in vegetarian person. Matthews JH et al had studied the megaloblastic anemia in 27 Asian patients and found 22 patients had nutritional deficiency of Vitamin B_{12} and 5 patients had pernicious anemia [15]. In his study 26 patients were Hindu vegetarian and only one patient was Muslim. He concluded that nutritional deficiency of vitamin B_{12} is the most common cause of megaloblastic anemia in Hindu. In our study there were 49 Hindus i.e. 81.67% which may explain the higher incidence of megaloblastic anemia in our study.

Macrocytic anemia is common in liver disorders. Macrocytic anemia was found to be associated with the severity of liver impairment and was proposed as a predictor for short-term mortality in patients with HBV-related decompensated cirrhosis in study done by Yang et al [9]. McPhedran et al [13] has also observed liver disorders as the second commonest cause. Unnikrishnan V et al [14] found liver disorders in 15% cases and the third commonest cause in their study.

Bone marrow disorders (including aplastic anemia, MDS and acute leukemia) accounted for 6 cases in our study. Davidson RJ et al [1] have observed 30 cases of hematological malignancy (out of 200 cases).

Drug therapy is a common cause of macrocytosis. Drugs cause megaloblastic anemia by impairing the cellular availability or the utilization of folic acid or vitamin B_{12}. This could be caused by interference with absorption, plasma transport, or delivery of folate or vitamin B_{12}, competition for reducing enzymes, end-product inhibition of co-factor- mediated reactions, or physical destruction of the vitamins [16]. Several drugs have been implicated to cause macrocytosis by different authors including anti epileptics, anti retroviral, chemotherapy, sulphonamides, metformin etc [1, 14].

CONCLUSION

Macrocytosis is a common abnormality detected in complete blood count and peripheral blood smear. Megaloblastic anemia due to vitamin B_{12} deficiency is the commonest cause of macrocytosis but the non-megaloblastic macrocytosis is caused by multiple causes. Macrocytosis without anemia may be the early indicator of vitamin deficiency. Presence of macrocytic anemia in a patient with chronic liver disease is an indication of severe liver impairment. So, early recognition of the underlying disease helps in proper and timely management of the patients.

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