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Macrocytic anemia: A review

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Abstract

Anemia is the lower level of hemoglobin concentration in men and women due to various reasons. There are many types of anemia depending upon how they are developed. One type of anemia is macrocytic anemia. In macrocytic anemia the RBCs are larger than the normal (macrocytosis) with MCV about 110 fl. The normal value of MCV is 80-100 FL. Macrocytosis either associated with anemia or it is without anemia. Because sometimes RBCs are larger due to some other reasons i.e. in pregnancy, new borne babies and infants. There are two categories of macrocytic anemia. 1) Megaloblastic and 2). Non-megaloblastic. Megaloblastic anemia is associated with bone marrow in which DNA synthesis is impaired due to nutritional deficiencies such as folic acid and vitamin B₁₂. While non-megaloblastic anemia is associated with general circulation. It is not related to nutritional deficiencies. Alcohol, liver disease and some other problems cause non-megaloblastic anemia. In megaloblastic anemia large oval shaped RBCs are present in bone marrow while in non-megaloblastic anemia large round shaped RBCs are present in general circulation. Their symptoms and treatment vary depending upon the type of anemia.

Keywords: Megaloblastic anemia, non-megaloblastic anemia, macrocytic anemia, vitamin B₁₂ deficiency, macrocytosis

Introduction

Anemia can be defined as that circulating erythrocyte mass is not adequate to prevent tissue hypoxia. Anemia occurred due to decreased production of RBC, increased destruction of RBC or due to blood loss. If the anemia occurred due to nutritional deficiency or due to disturbance in cell maturation then it is called macrocytic anemia ^[1]. Macrocytosis is a blood condition in which blood cells are larger and thick (macrocytes) and the mean cell volume raise to about 110 fl ^[4]. Normal value of mean corpuscular volume (MCV) should be 80-100 fl. The value of MCV varied by age and reference laboratory ^[3]. The prevalence of macrocytic anemia varied from 1.7% to 3.6% ^[5]. The causes of macrocytosis varies. In primary cases vitamin deficiencies and alcohol use are the primary causes. After evaluation even some cases remained unexplained ^[2]. Macrocytic anemia can be diagnosed by peripheral blood smears and red blood cells indices. Peripheral blood smears is more useful to diagnose early macrocytic anemia while red blood cell indices can't be diagnose early macrocytic anemia. Mean corpuscular volume underestimate the macrocytosis when it is compared with peripheral blood smear. In the case of hyperglycemia, leukocytosis and cold agglutinins the MCV level increased so it is not accurate to diagnose macrocytic anemia. The value of MCV also change whenever problem with instrument or blood left at room temperature for several hours. The MCV value greater than normal required special identification either it is due to macrocytic anemia or associated to any other problem. Macrocytosis may be due to anemia or without anemia ^[3].

Macrocytosis without Anemia

Large red blood cells are not always associated with anemia. The erythrocytes of new borne babies and infants are also larger than the normal about 108 FL. Large erythrocytes may also present in pregnant women. Macrocytosis without anemia is not a major problem and can be identified by peripheral RBC indices. Sometimes macrocytic anemia is associated with genetic predisposition in family members ^[3].

Macrocytosis associated with Anemia

In the case of macrocytosis with anemia abnormally large RBC present in blood. This abnormality of RBC can be recognized by peripheral blood smear ^[3].

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There are two categories of macrocytic anemia.

- Megaloblastic Anemia
- Non- Megaloblastic Anemia

This categorization is important to understand the etiology of anemia. The true mechanism of macrocytosis is still unknown and the difference between megaloblastic and non-megaloblastic anemia is completely un-natural [18].

Megaloblastic Anemia

Megaloblastic anemia increased from last two decades. It is most common in underdeveloped countries and less common in developed countries [12]. Megaloblastic anemia related to megaloblastic changes in bone marrow [10]. In megaloblastic anemia hemoglobin level is decreased with increased MCV [7].

Causes of Megaloblastic Anemia

Folic acid and vitamin B₁₂ are the major causes of megaloblastic anemia [15]. Folic acid and vitamin B₁₂ deficiency leads to impaired DNA synthesis, ineffective erythropoiesis, and intramedullary hemolysis. Due to these condition the level of unconjugated bilirubin and serum LDH (lactate dehydrogenase) increased. LDH is a tissue marker breakdown and present in RBC. LDH released into circulation when destruction of RBCs occur. High level of LDH present due to tissue breakdown. High LDH level is one of the tool to identify the megaloblastic anemia. Increased serum LDH also seen in other condition for example in the case of hemolytic anemia [7]. Vitamin B₁₂ deficiency also leads to thrombocytopenia in which reduction of platelet level to below normal [11]. For the identification of Megaloblastic anemia bone marrow examination is necessary [9]. In megaloblastic anemia DNA synthesis is affected while RNA synthesis remain unaffected. Folic acid and vitamin B₁₂ are necessary for the synthesis of purine and thymidylate, and their deficiency prevent DNA synthesis. Synthesis of DNA may be delayed when certain drugs are used such as purine antagonists, thymidylate antagonists and folate antagonist [6]. The inhibitors for reverse transcriptase interfere with DNA and cause macrocytosis. Most patients with HIV medication have macrocytosis without anemia. It means no treatment is necessary. The patients who have the evidence of blood loss, or increased cell destruction have macrocytosis. Myeloproliferative disorders is the common cause of macrocytosis in old people [18]. Macrocytosis also developed due to chronic obstructive pulmonary disease but it is not known whether the lung disease itself cause MCV to rise or some other diseases [19].

Significance of vitamin B₁₂

Vitamin B₁₂ have major role in the production of red blood cells. Without vitamin B₁₂ DNA synthesis become defective so red blood cell morphology is changed. The second important function of vitamin B₁₂ is role in the development of nerve cells. Without vitamin B₁₂ the myelin sheath is not formed and cause various nervous system disorders. And proper cycling of proteins also depends upon the vitamin B₁₂ [16].

Causes of vitamin B₁₂ deficiency

Vitamin B₁₂ deficiency is more noticeable in elder people due to less absorption of vitamin B₁₂ with age. Vitamin B₁₂ deficiency also related with poor diet and mostly dependent on vegetarian diet [9]. Because bulk of Vitamin B₁₂ have

animal origin. So animal foods are important to obtain vitamin B₁₂. One study shows that cobalamin and vitamin level is lower in those mother's milk who are purely vegetarian [10]. In some cases depleted ascorbic acid and infection are the reason for the vitamin B₁₂ and folic acid deficiency. Some relation is present between the infections and ascorbic acid on the metabolism of folic acid and vitamin B₁₂. Requirement of folic acid is increased by the deficiency of ascorbic acid. This mechanism is more important in infants [8].

Pernicious Anemia

One other major cause of megaloblastic anemia is pernicious anemia which is autoimmune gastritis from damage of gastrointestinal parietal cells and absence of intrinsic factor that is required for the absorption of vitamin B₁₂. Other disorders related to pernicious anemia are disease of thyroid gland, vitiligo and type 1 diabetes mellitus. Pernicious anemia is most common in Africa and Europe [13].

Tran's cobalamin II deficiency

Tran's cobalamin II deficiency is an autosomal recessive disease which leads to defective intestinal absorption of vitamin B₁₂. The main symptom of Tran's cobalamin II deficiency is megaloblastic anemia. TCII is a plasma protein which bind vitamin B₁₂ and facilitate the uptake by cell. TCII have 43 KDa molecular mass and is non-glycosylated secretory protein, its plasma membrane receptor is glycosylated and important for vitamin B₁₂ transportation. Vitamin B₁₂ transportation is a very complex process and it binds to almost 5 different molecules for its transportation in circulation. First of all it binds to haptocorrin in the stomach, then bind with intrinsic factor in stomach then uptake by epithelial cells and proteolytic release of Vitamin B₁₂ and bind to TCII. Then TCII receptors transport it to cell membrane. So when TCII deficiency the proper transportation of Vitamin B₁₂ can't be occurred and cause megaloblastic anemia [14].

HIV medication

Inhibitors of Reverse transcriptase e.g. lamivudine, stavudine, zidovudine cause macrocytosis by interfering with DNA synthesis. Most patients with HIV medication have macrocytosis without anemia. It means no treatment is necessary [18].

Diagnosis

Megaloblastic anemia is diagnosed by peripheral blood smear, complete blood count and bone marrow aspiration. Peripheral blood smear show large RBC (macrocytosis) [12]. The presence of large oval RBC with MCV >115 fl, anisocytosis, poikilocytosis and hypersegmented neutrophils show megaloblastic anemia with nutritional deficiency [3]. Erythrocytes are larger than the normal at every stage and have an open and finally dispersed nuclear material and the ratio of nucleus and cytoplasm is not same. In megaloblastic anemia of childhood cytopenias, bicytopenias, pancytopenia are common. There is delay in nuclear progression and cell maturation. In bone marrow bands and giant metamyelocytes are also present. Ineffective erythropoiesis, and premature cell death decrease the output from bone marrow and anemia occurred [12]. Reticulocyte count is obtained if there is any evidence of destruction of RBCs. In megaloblastic anemia bone marrow is hyper cellular and it show abnormal maturation and proliferation of different myeloid cells.

Erythrocyte precursors in bone marrow have large erythroblasts. Other myeloid cells also show morphological abnormalities. This ineffective erythropoiesis show increased LDH and bilirubin in the serum. However reticulocyte count is low due to maturation abnormalities. The patients who are not anemic don't require bone marrow examination [3].

Symptoms of megaloblastic Anemia

In megaloblastic anemia patients when they maintain a standing position the level of norepinephrine hormone is decreased so vasoconstriction force is decreased and as a result postural hypotension. Blood pressure is decreased in these patients but when they are treated with folic acid and vitamin B₁₂ their blood pressure steadily rises [9]. Most obvious features due to megaloblastic anemia are hyperpigmentation of knuckles and terminal phalanges and enlargement of spleen and liver [10] jaundice, tongue is beefy red and smooth weakness, irritability, poor appetite [12]. Tremors also seen in children of North and central India. Other cases related to megaloblastic anemia are developmental retardation, abnormal movement, psychomotor retardation and impairment of cognitive functions [10].

Treatment

Caution is more necessary in older people [20]. Cobalamin and folic acid are used mostly for its treatment. Megaloblastic anemia develop slowly and some patients adjust the low hemoglobin level and don't require transfusion. In severe and life threatening cases transfusion therapy must be required. For two weeks daily treatment of Cobalamin is required, then after week until the value come to be normal and then after month for whole life. Several other protocols recommended with cobalamin therapy. But the patients who have neurological complications because of cobalamin deficiency should be treated violently. Oral cobalamin also administered but the absorption can be varied and it is insufficient for some patients. Oral cobalamin given to hemophilia patients to avoid intramuscular injection and bleeding. The patients who have neurological complications should be given intramuscular cobalamin. Oral cobalamin is less costly and the patient can tolerate it. Folic acid (3-5 mg) directed orally, but if it is difficult than equivalent doses are directed by injection. During pregnancy, lactation and perinatal period, folic acid should be recommend prophylactically. Folic acid supplements and fortification of food have been suggested to reduce the menace of pancreatic, cervical and colon cancer. Folic acid supplements specified in elder people and at end stage of renal failure. Folic acid therapy should not be institutive if cobalamin deficiency have not been ruled out. Although patients feel better after starting the therapy but monitoring is necessary. High level of LDH and bilirubin must fall rapidly. Persistent high level of LDH is the indication of failure of therapy. Leukocyte and platelet count restored to normal but hyper segmented neutrophil may persist for 10-14 days. Serum potassium level may fall during the treatment of severe cases and it leads to death. So monitoring of potassium is necessary and supplements should be given during therapy [21].

Non-Megaloblastic Anemia

In non-megaloblastic anemia DNA synthesis is normal. It is associated with general circulation. In non- megaloblastic anemia RBCs are round in shape. It includes accelerated erythropoiesis, alcoholism, liver disease, and hypothyroidism. But mainly it is associated with hemolytic anemia in which

due to deposition of cholesterol in RBCs membrane the cells become large and entrap in spleen and then destroyed [17].

Causes of non-megaloblastic Anemia

Liver disease

Macrocytosis due to liver disease have cholesterol deposition on their RBC membranes. The reticulocyte (immature red blood cells) are 20% larger than mature red blood cells in macrocytosis [6]. Large erythrocytes or acanthocytes are developed with spike like projections and irregular surfaces and vary in length, width and distribution [17].

Alcohol consumption

The people who are from nutritional deficiencies have impaired hematopoiesis when they intake alcohol. Chronic excessive alcoholism reduce the production of red blood cells and the erythrocytes that are larger than the normal. The red blood cells structure is also abnormal and the number of platelets also reduced. In people who use alcohol the size of RBC and MCV are larger than the people who does not use alcohol. However MCV alone is not appropriate to diagnose the non-megaloblastic anemia. The presence of large red blood cells (RBC) in blood is the indication of many other problems in addition to alcohol. For the identification of macrocytosis physician observe the blood under microscope to identify the structure of blood cells for each disorder. Thus the enlarged red blood cells in non-megaloblastic anemia are uniformly round while in case of megaloblastic anemia the red blood cell are oval in shape. People who drink excessive alcohol develop large RBC even in the absence of other factor that are responsible for RBC enlargement such as folic acid deficiency and alcohol liver disease. Alcohol abuse is a disorder mostly associated to macrocytosis, more than 80 % of men and 46% women have been found alcoholics [17]. The patients who have folate or vitamin B₁₂ deficiency should obtain dietary education on the preparation and selection of food. Patients take diet that are rich in folic acid such as melons, bananas, lemon, lettuce, spinach, broccoli, asparagus and mushrooms. Foods should not be overcooked and not diluted in water. To avoid vitamin B₁₂ deficiency dairy products and eggs must be included in diet. Patients must be know that there is a little quantity of folic acid in goat milk [21].

Conclusion

Vitamin B₁₂ and folate are major factors of causing megaloblastic anemia. Inadequate intake of food, overcooking of food, and poor absorption cause Vitamin B₁₂ and folate deficiency. And nutritional deficiencies are more common in Pakistan. So medical communities should seriously contribute in screening of patients who have minor symptoms if anemia.

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