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A Review on Macrocytic Anemias in Geriatric Patients – Etiology, Diagnosis and Treatment Modalities

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ABSTRACT

In primary care, anaemia is one of the most frequent health concerns. Macrocytosis in adults is defined as a mean corpuscular volume (MCV) of red blood cells (RBCs) more than 100 femtoliter (fL). Megaloblastic and nonmegaloblastic anemias are the two types of macrocytic anaemia. Nonmegaloblastic macrocytic anaemia is caused by diseases such as myelodysplastic syndrome (MDS), liver dysfunction, alcoholism, hypothyroidism, certain drugs, and less commonly inherited DNA synthesis disorders. Megaloblastic anaemia is caused by a deficiency or impaired utilisation of vitamin B12 and/or folate, whereas nonmegaloblastic macrocytic anaemia is caused by a variety of diseases such as MDS, liver dysfunction, Macrocytic anemias are treated with cause-specific medications, and distinguishing nonmegaloblastic anaemia from megaloblastic anaemia is critical. Because MDS and myeloid neoplasms are more frequent among the elderly, primary care physicians may see more instances of macrocytic anaemia in the near future as the population of the elderly grows. A hematology consultation may be necessary if MDS is suspected coupled with leukocytopenia and/or thrombocytopenia with anaemia.

Keywords: Macrocytic Anemias, Myelodysplastic Syndrome, Nonmegaloblastic Anemia, Pernicious Anemia

Introduction

One of the most prevalent illnesses detected by health care providers is anaemia. In 2010, the global prevalence of anaemia was 32.9 %, affecting over 2.2 billion people. [1] Anemia is defined as a haemoglobin (Hb) level of less than 13 g/L in males, less than 12 g/L in nonpregnant women, and less than 11 g/L in pregnant women and the elderly, according to the World Health Organization (WHO). Anemia is caused by a variety of factors, including age, gender, and geographic location, with iron deficiency anaemia being the most frequent. [1] For differential diagnosis, the red cell indices of Wintrobe [2], which are determined from red blood cell count, haemoglobin concentration, and hematocrit, can be used to classify the kind of anaemia. The mean corpuscular volume (MCV) is computed as hematocrit percentage 10/RBC count (106/l), with MCV >100 fL indicating macrocytic anaemia.

Despite the fact that macrocytic anemias are uncommon among general practitioners, a report from a family practice group found macrocytosis in 2 % to 4 % of patients [3], and a study of 1784 randomly selected older adults living at home discovered macrocytosis in 6.3 % of men and 3.3 % of women. [4] Because older persons sometimes have comorbidities, the reasons of anaemia are multifaceted. Hematologic malignancy and iron deficiency anaemia accounted for 22 % and 12 % of the older adult patients with anaemia, respectively, according to the Stanford study, while the aetiology of anaemia was unclear in 35 % of the patients. [5] With the predicted growth in the elderly population, the number of instances with macrocytic anaemia seen by primary care physicians is expected to rise. As a result, the diagnosis and management of macrocytic anemias in adults are summarised in this review.

Etiology

Macrocytic anaemia is defined as either megaloblastic or nonmegaloblastic, depending on the etiology. Megaloblastic anaemia is caused by the deficiency of vitamin B12 or folate. Nonmegaloblastic anaemia can be caused by liver disease, alcoholism, myelodysplastic syndrome (MDS), or hypothyroidism, among other things. The most common causes of macrocytosis vary by geography and setting. In New York, for example, 37 % of instances detected in hospitalised patients were connected to medication. [6] For human immunodeficiency virus (HIV) infections, antiretroviral treatment (ART) accounted for 13% of the total. [6] In outpatients over 75 years of age in Finland, the most prevalent causes of macrocytic anaemia were alcoholism (65%) [7] and vitamin B12 or folate insufficiency (28%) [8].

Vitamin B12 Deficiency

Megaloblastic anaemia is most commonly caused by a lack of vitamin B12. Insufficient dietary intake, such as in the case of vegetarians or malnutrition, malabsorption due to the absence of intrinsic factor caused by pernicious anaemia or following gastric surgery, congenital disorders, such as transcobalamin II deficiency, or exposure to nitrous oxide are all causes of vitamin B12 deficiency.

Pernicious anaemia (61%) is the most prevalent cause of megaloblastic anaemia, according to one Japanese research, followed by vitamin B12 insufficiency owing to gastrectomy (34%), vitamin B12 deficiency due to other reasons (2%), and folate deficiency (2%). [9] Vitamin B12 is found in animal sources, and a daily dose of 3-30 g is recommended.

Vitamin B12 binds to the gastric parietal cells' intrinsic factor and is absorbed in the terminal ileum. Vitamin B12 works as a cofactor in the biochemical activity that creates methionine from homocysteine once it has been absorbed. Folic acid is transformed into its active form as a consequence. Active folic acid is insufficient when vitamin B12 is deficient. As a result, the intracellular process involving folic acid's coenzyme form is harmed. As a result, both vitamin B12 and folate deficiency hinder DNA synthesis. Because the liver stores a substantial quantity of vitamin B12, it takes 5–10 years for clinical symptoms to appear after a reduction in vitamin B12 consumption or absorption. [10]

Fatigue, headache, palpitations, and dyspnea are indications and symptoms of megaloblastic anaemia caused by vitamin B12 deficiency, and neurological symptoms such as dysesthesia and hypoesthesia may also be present. Ataxia, reduced proprioception, and vibratory feeling may all be present in severe cases of subacute combined degeneration. In most cases, folate insufficiency does not cause neurologic symptoms. Anemia and macrocytosis are not always symptoms of vitamin B12 deficiency. Hunter's glossitis and grey hair are two further signs.

In extreme instances, peripheral blood smears demonstrate macrocytic anemias and pancytopenia, as well as hypersegmented neutrophils. Impaired nuclear differentiation causes megaloblastic alterations in erythroblasts and large metamyelocytes in bone marrow. Blood biochemistry reveals higher amounts of indirect bilirubin and lactate dehydrogenase (LDH), as well as lower levels of haptoglobin. Parenteral vitamin B12 therapy is used to treat vitamin B12 deficiency, and haematological levels usually recover to normal within one month. Lifelong medication is required for individuals who have a persistent loss in their ability to absorb dietary vitamin B12, such as those who have pernicious anaemia or had a complete gastrectomy. [10] Iron deficiency may occur during hematopoietic healing. Although it is not a proven treatment, it has recently been shown that oral treatment is helpful because 1–5% of vitamin B12 absorption in the terminal ileum occurs by passive diffusion, which does not need intrinsic factor. [10]

Pernicious Anemia

Pernicious anaemia is responsible for 20% to 50% of vitamin B12 deficiency in adults [11] and is linked to autoimmune gastritis, which results in the loss of stomach parietal cells and a lack of intrinsic factor. [12] The frequency of pernicious anaemia in North Europeans and Caucasian Americans is estimated to be 10-50 per 100000 people. In comparison to the West, the prevalence of pernicious anaemia in Japan is low, at 1-5 per 100 000 people [13]. Autoimmune metaplastic atrophic gastritis (AMAG), which mostly affects the stomach body and fundus, causes pernicious anaemia. Antibodies against the hydrogen potassium adenosine triphosphatase (H+/K+-ATPase) proton pump are identified in antigastric parietal cell autoantibodies in pernicious anaemia. Helicobacter pylorus (H. pylori) is not often thought to be linked to AMAG. Based on their finding that the frequency of H. pylori infection was 87.5 % in patients under the age of 20, Hershko et al. suggested that H. pylori might be a trigger of AMAG and pernicious anaemia. [14] Furthermore, molecular mimicry between H. pylori antigens and gastric H+/K+-ATPase has been proposed as a possible cause of AMAG. [15] When parietal cells are destroyed, acid production and intrinsic factor secretion are reduced, and autoantibodies against intrinsic factor prevent vitamin B12 absorption. Gastrin production from antral G cells rises as a consequence, and hypergastrinemia causes oxyntic mucosal cell growth, including enterochromaffin like cells and parietal cells. [16] Pernicious anaemia has symptoms that are similar to other vitamin B12 deficiencies, but it is also linked to autoimmune illnesses such as Type 1 Diabetes, Autoimmune Thyroiditis, and Addison's Disease. The anti intrinsic factor antibody test has a sensitivity and specificity of 50 %, 70 %, and higher than 95 %, respectively. [17] The antigastric parietal cell antibody test has a sensitivity and specificity of more than 90% and 50%, respectively. [18] Vitamin B12 is given to people with pernicious anaemia throughout the rest of their lives. Gastric adenocarcinoma and carcinoid tumours are quite common in patients with pernicious anaemia. [19] The existence of pernicious anaemia, the degree of mucosal atrophy, intestinal metaplasia, illness duration, and being over 50 years old are all significant risk factors for the development of gastric cancer in AMAG. [16] Patients with pernicious anaemia should have their stomachs examined on a regular basis.

Folate Deficiency

Green vegetables and animal products (such as liver), contain folic acid. Adults should consume 240 grammes of folic acid per day, while pregnant or lactating women should consume roughly 400 grammes per day. Folate deficiency during pregnancy may raise the chance of congenital neural tube stenosis. Both passive diffusion and active uptake are used to absorb folic acid in the upper jejunum. Nutritional deficiency (e.g., poor diet, drunkenness), malabsorption (e.g., celiac disease, inflammatory bowel disease), higher needs (e.g., pregnancy, breastfeeding, chronic hemolysis), and medicine can all produce folate deficiency (eg, methotrexate, trimethoprim, phenytoin). Because blood folate levels fluctuate with food consumption, researchers have found that measuring RBC folate levels, which represent tissue folate reserves, is more dependable. [20] If the reason of folate insufficiency is nutritional inadequacy or increased nutritional needs, patients are generally treated with oral folic acid.

Myelodysplastic Syndrome

MDS is a clonal hematopoietic stem cell condition marked by cytopenia, myelodysplasia, inefficient hematopoiesis, and a higher risk of developing acute myeloid leukaemia (AML). [21] In Japan, the frequency is at 3 per 100000 people. Six people with MDS were detected in a study of 124 patients

aged 75 and over who had a high MCV (>95 fL). [8] MDS is caused by oncogenic mutations that are acquired in stages. In 30 to 50 % of MDS patients, clonal chromosomal abnormalities are seen, as well as gene alterations. Recurrent somatic mutations in genes involved in epigenetic regulation (TET2, ASXL1, EZH2, DNMT3A, IDH1/2), RNA splicing (SF3B1, SRSF2, U2AF1, ZRSR2), DNA damage response (TP53), transcriptional regulation (RUNX1, BCOR, ETV6), and signal transduction (CBL, NRAS, JAK2) have been identified in MDS patients. [22] Patients with MDS may experience anemia, thrombocytopenia-related bleeding, and infection or fever as a result of neutropenia. A study of the peripheral blood demonstrates cytopenia due to inefficient hematopoiesis. The WHO classification method uses a mix of morphology, immunophenotype, genetics, and clinical factors to classify MDS. Treatment options are determined on the MDS subtype and the patient's age. Allogeneic hematopoietic stem cell transplantation may be used to treat patients under the age of 55 who have significant bone marrow failure or are at high risk of acquiring AML. Patients over 65 years old or with low-risk conditions, on the other hand, are usually treated with supportive treatment, such as blood transfusions and antibiotics for bacterial infections.

Alcoholism

The most common cause of macrocytic anaemia is alcoholism. Chronic alcohol use of more than 80gm per day has negative consequences for the hematopoietic system. [23] Approximately 90% of alcoholics have macrocytosis before they develop anaemia (MCV between 100 and 110 fL). [24] Although diagnosing alcoholism in people with macrocytosis can be challenging, the Michigan Alcoholism Screening test and gamma-glutamyltransferase levels have been reported to be the two most sensitive tests for detecting alcoholism. [25] The preceding tests may be beneficial in patients with increased MCV, taking into account the risk of alcoholism. Abstinence from alcohol quickly brings high MCV [26] levels back to normal.

Hypothyroidism

Anemia caused by hypothyroidism is either normocytic or macrocytic in nature. A decrease in thyroid hormone production may induce anaemia because thyroid hormone enhances the development of erythropoietin and influences hematopoiesis.

Drugs

Many medicines produce megaloblastic anaemia by affecting folic acid or vitamin B12 availability or usage in the body. Interference with folate or vitamin B12 absorption, plasma transport, or distribution, competition for reducing enzymes, end product inhibition of cofactor mediated processes, or physical destruction of the vitamins might all contribute to this. [27] Hydroxyurea, methotrexate, zidovudine, azathioprine, antiretroviral medications, valproic acid, and phenytoin are all common medicines that induce macrocytosis.

Differential Diagnosis of Macrocytic Anemias

When macrocytosis is suspected, the differential diagnosis should begin with measuring vitamin B12 and folate levels in the blood. Red blood cells that are bigger than the nucleus of a tiny lymphocyte are known as macrocytic cells. Although macroovalocytes, anisocytosis, and hypersegmented neutrophils imply megaloblastic anaemia due to vitamin B12 or folate insufficiency, similar morphological abnormalities can also be found in MDS or drug-induced DNA synthesis problems. Macrocytic anaemia with a similar appearance is more typically caused by hereditary DNA synthesis abnormalities such Lesch-Nyhan syndrome and transcobalamin deficiency. Vitamin B12 deficiency is quite probable if blood vitamin B12 levels are less than 200 pg/mL. [29] Vitamin B12 deficiency is rare if blood vitamin B12 levels are more than 300 pg/mL. [12] However, recent investigations have found that when current immunoenzymatic approaches are applied, many individuals with pernicious anaemia have normal or erroneously high vitamin B12 levels. [30] If blood vitamin B12 levels are between 200 and 300 pg/mL, metabolite testing should be held for individuals who are most likely to be deficient in vitamin B12. In vitamin B12 shortage, both homocysteine and MMA concentrations in the blood are raised, whereas only homocysteine is high in folate deficit. [31] Folate deficiency may be effectively ruled out if the blood folate level is more than 4 ng/mL, whereas a serum folate level below 2 ng/mL is diagnostic for folate deficit. Tropical sprue or gluten-sensitive enteropathy can produce combined vitamin B12 and folate insufficiency. A reticulocyte count should be acquired once vitamin B12 or folate insufficiency has been ruled out. Reticulocytes are nonnucleated, immature erythrocytes. Reticulocytes make up around 1% of red blood cells in general. Acute blood loss or hemolysis is suspected if the absolute reticulocyte count is more than 100000/µl. Hemolytic anaemia is indicated by high levels of indirect bilirubin and LDH, as well as low levels of haptoglobin. Acute blood loss should be considered in the differential diagnosis if hemolysis is not observed. Absence of reticulocytosis points to liver disease, hypothyroidism, or MDS as causes. Macrocytic target cells, hypolobulated or hypogranular neutrophils, improperly granulated platelets, and monocytosis are all typical findings on peripheral blood smears in liver illness. When MCV is extremely high (>130 fL), the differential diagnosis is narrowed to include HIV infection, hydroxyurea usage, and vitamin B12 or folate insufficiency. [32] When there is considerable reticulocytosis, the MCV levels may be artificially increased due to the high reticulocyte volume. [33] Hyperglycemia, severe leukocytosis, and cold agglutinins can also produce erroneous macrocytosis. [20]

Conclusions

Because macrocytic anemias are more frequent in elderly people, primary care physicians may see more cases of macrocytic anemias in the near future than they have in previous decades as the population ages. Despite the fact that macrocytic anemias can have a variety of causes, MDS is one of the most common among the elderly, and clonal hematopoiesis with somatic mutations identical to those found in MDS patients has been verified in 10% of those over 65 years of age and who have no evident haematological abnormalities. [34] A visit with a haematologist is indicated when the reason of anaemia cannot be established despite efforts using noninvasive diagnostic tests and treatments.

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