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Megaloblastic Anemia

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1. Abstract

Folic acid and cobalamin are B-group vitamins that play an essential role in many cellular processes in the body. Deficiency in one or both of these vitamins causes megaloblastic anaemia. This is a disease characterized by the presence of megaloblasts. Megaloblasts occur when inhibition of DNA synthesis causes abnormal maturation between the nucleus and the cytoplasm of the cell. Megaloblastic anemia causes macrocytic anemia and intramedullary hemolysis. The most common causes are folate (vitamin B9) deficiency and cobalamin (vitamin B12) deficiency. Megaloblastic anemia can be diagnosed based on characteristic morphologic and laboratory findings. Therapy involves treating the underlying cause eg, with vitamin supplementation in cases of deficiency.

2. Introduction and History

Nutritional anemias are the common causes of anemia in any population. Though iron deficiency anemia is the commonest cause, megaloblastic anemia due to folic acid or vitamin B12 deficiency must be considered as well.

3. Case Report

A 50-year-old lady doctor reported to me with severe anemia (Hb 4 gm/dl). Initially considered to be due to iron deficiency anemia, non-response to iron treatment, raised suspicion of other possibilities. On further probing it was found she was a pure vegetarian; even hardly took milk (which is usually a good source of Vitamin B12). Blood peripheral smear showed macro-ovalocytes and hyper segmented neutrophils. Serum cobalamin level was found to be significantly low. Patient was treated with Injection cobalamin 1000µg daily for several days and her reticulocyte count rose rapidly and hemoglobin shot up rapidly. Her hemoglobin normalized within four weeks. Megaloblastic anemia was first described by Addison in 1849. In 1880, Ehrlich identified them as precursors of giant blood cells; thus named megaloblastic anemia.

4. Definition

The megaloblastic anemias are disorders caused by impaired DNA synthesis due to impaired DNA synthesis because of deficiencies of vitamin B12 or folic acid.

4.1. Pathogenesis of Megaloblastic Anemia

Megaloblasticstic anemia results from abnormal maturation of hematopoietic cells due to impaired DNA synthesis. The cobalamin (Cbl) and folic acid are two essential vitamins for DNA biosynthesis. All proliferating cells will exhibit megaloblastosis; In the hematopoietic system this results in abnormal nuclear maturation with normal cytoplasmic maturation, apoptosis, ineffective erythropoiesis, intramedullary hemolysis, pancytopenia and typical morphological abnormalities in the blood and marrow cells.

4.2. Aetiology

It is multifactorial and may result from dietary deficiency, impaired absorption, and transport or impaired utilization of these vitamins in DNA synthesis.

4.3. Prevalence and Causative Factors

On analyzing the literature, it is found that dietary and pregnancy related folate deficiency are probably the most common causes of megaloblastic anemias. The frequency of pernicious anemia (PA) is 0.25 – 0.5 cases per 1000 persons in their seventh decade of life. However, frequency of PA is reported to be higher in Sweden, Denmark, and the United Kingdom (100-130 cases per100,000 population). In a study conducted in Hong Kong on 84 consecutive Chinese patients with megaloblastic anemia (48 males and 36 females), the median age at presentation was 67 years, and vitamin B12 deficiency was found in all cases and none had folate

deficiency.

4.4. Cobalamin Deficiency

A. Vitamin B12 Deficiency

Vitamin B12 is produced by microorganisms and is found almost exclusively in foods of animal origin. Normal body stores of vitamin B12 are 3 to 5 mg, and the recommended adult daily intake is 6-9 μg. Causes of vitamin B12 deficiency are listed below. Dietary deficiency of vitamin B12 occurs less frequently than folate deficiency because body stores can last for years owing to efficient enterohepatic recycling mechanisms. Although uncommon, dietary B12 deficiency can occur even in industrialized countries in strict vegans and vegetarians, or in breastfed infants of mothers with vitamin B12 deficiency. Dietary absorption of vitamin B12 is a complex process that begins with haptocorrin (also known as transcobalamin I or R-binder) production by the salivary glands. When food is digested in the stomach by gastric acid and pepsin, free vitamin B12 is released and binds to haptocorrin. Simultaneously, gastric parietal cells secrete intrinsic factor, which cannot interact with the vitamin B12-haptocorrin complex. Not until food moves into the duodenum, where trypsin and other pancreatic enzymes cleave haptocorrin, is vitamin B12 free to bind to intrinsic factor. The resultant vitamin B12-intrinsic factor complex binds to the cubam receptor on the mucosal surface of enterocytes in the ileum. From there, vitamin B12 is transported into the circulation by multidrug resistance protein 1, where it is readily bound by its transport protein transcobalamin II. The vitamin B12-transcobalamin complex then binds to the transcobalamin receptors on hematopoietic stem cells (and other cell types), allowing uptake of the complex, with subsequent lysosomal degradation of transcobalamin. Free vitamin B12 is then available for cellular metabolism. Nearly every step of this pathway can be disrupted in various pathologic states, but lack of intrinsic factor secondary to pernicious anemia is the cause of vitamin B12 deficiency in most cases. Chronic atrophic autoimmune gastritis is an autoimmune process directed specifically at either gastric parietal cells or intrinsic factor, or both. Parietal cell damage leads to reduced production of gastric acid and intrinsic factor, accompanied by a compensatory increase in serum gastrin levels. Decreased intrinsic factor leads to reduced absorption of dietary vitamin B12, resulting in pernicious anemia. Chronic atrophic autoimmune gastritis affects the body and fundus of the stomach, replacing normal oxyntic mucosa with atrophic-appearing mucosa, often with associated intestinal metaplasia.

B. Causes of Vitamin B12 Deficiency Common Causes (related to malabsorption)

Autoimmune gastritis (pernicious anemia) Celiac disease, Inflammatory bowel disease Surgical gastrectomy gastric bypass ileal resection.

C. Less Common Causes

Nutritional (strict vegans, breastfed infants of mothers with vitamin B12 deficiency) Diphyllobothrium latum infection Pancreatic in sufficiency Drug effect (metformin, proton pump inhibitors) Inherited disorders affecting intrinsic factor Rare inherited disorder (eg, methylmalonic acidemia, transcobalamin II deficiency).

D. Physiologic Considerations

Animal products (meat and dairy products) are only dietary source of cobalamin for humans. The minimal daily requirement is 6μg/day to 9μg/day. Total body stores are 2-5 mg of cobalamin (Cbl), approximately half of which is in liver.

E. Clinical Features of Cobalamin Deficiency

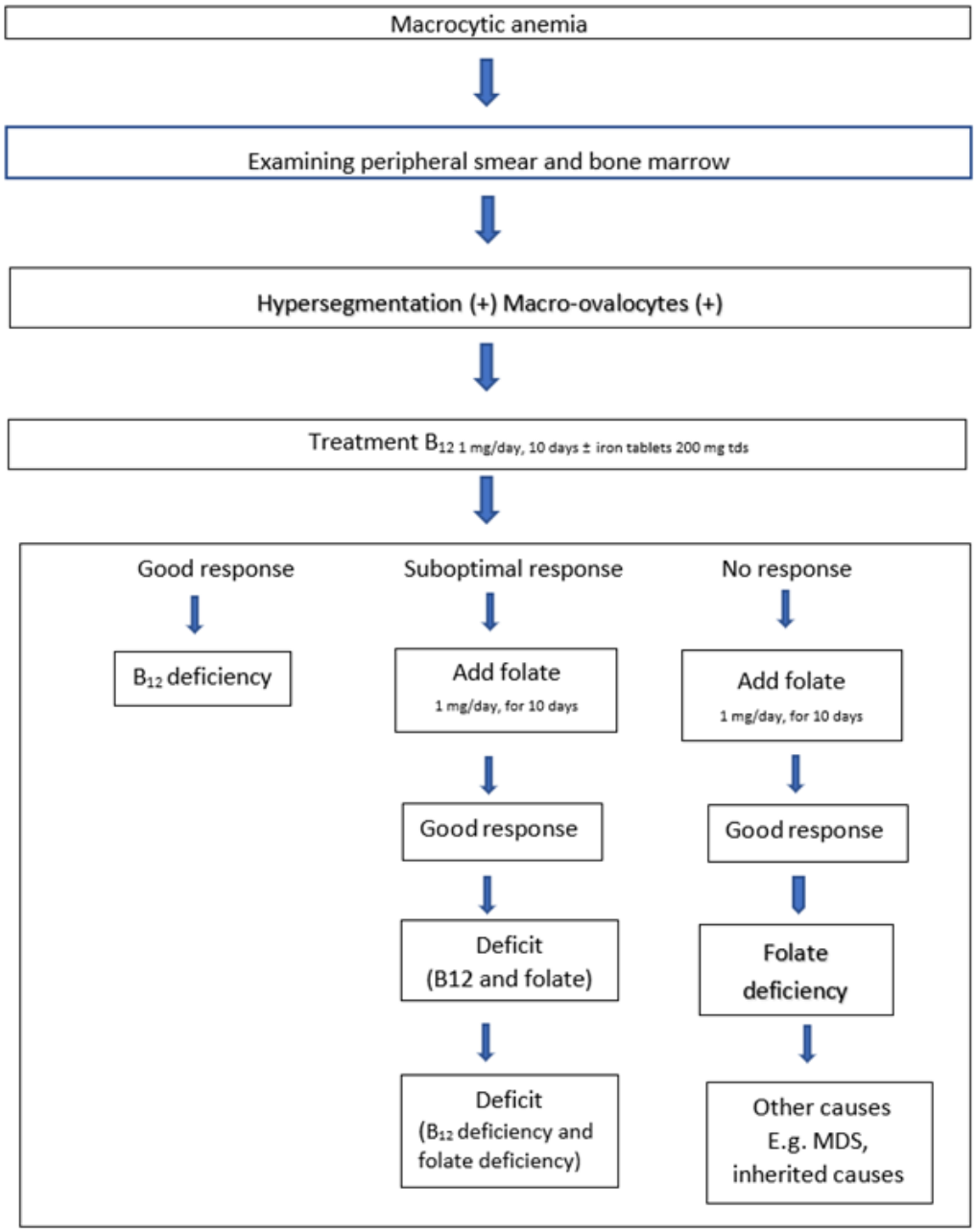
The classic picture of Cbl deficiency due to pernicious anemia is mentally sluggish person with a shiny tongue (atropic glossitis) and a shuffling broad gait. This classic picture is now replaced by more subtle presentation. Because cobalamin is required for all rapidly growing cells, including enteric mucosal cells and epithelial cells of skin, patients with cobalamin deficiency may complain of glossitis, vaginal atrophy and malabsorption; they often have diffuse hyperpigmentation, particularly increased over the knuckles. The patients may have neuro-psychiatric problems consisting of paresthesia, numbness, weakness, impaired memory and personality changes.

When the anemia is severe, there may be thrombocytopenia and neutropenia (i.e. pancytopenia).

F. Neurologic Abnormalities

Neuropsychiatric features Vitamin B12 deficiency can cause subacute combined degeneration of the dorsal and lateral columns of the spinal cord. Patients may experience bilateral and symmetrical paresthesia. Subacute combined degeneration of spinal cord is the characteristic abnormality resulting from demyelination of dorsal and lateral columns. This lesion is specific for Cbl deficiency. The neuropathy is symmetrical, affecting the legs more than the arms. It begins with paresthesia and ataxia associated with loss of vibration and position and progress to severe weakness, spasticity, clonus and paraplegia. Other neurologic abnormaities that can be seen are axonal degeneration of peripheral nerves. Other symptoms include memory loss, irritability and dementia. Patients may present with Lhermitte's syndrome, a shock-like sensation that radiates to the feet during neck flexion.

It is important to note that patients with neurologic manifestations due to Cbl deficiency may not necessarily be anemic or may not even show macrocytic red cell indices.



Algorithm: Algorithmic approach for a tentative diagnosis

4.5. Folic Acid Deficiency

A. Physiologic Considerations

Folate occurs in animal products and leafy vegetables in the polyglutamate form. Normal daily requirement is about 200-400 µg/day; in pregnancy and lactation, this increases to 500-800 µg/day. The most common cause of folate deficiency is nutritional due to poor diet and /or alcoholism. Body stores are small (5-10 mg) and individuals on a folate deficiency can develop megaloblastosis within 4-5 months.

Folate at physiologic level enters cells by binding to a folate receptor. Once inside the cell, folic acid is polyglutamated which is biologically active.

B. Causes of Folate Deficiency

- Alcohol abuse
- Pregnancy
- Hemolytic anemia
- exfoliative skin diseases
- drugs e.g. phenytoin, trimethoprim methotrexate
- malabsortion syndrome

C. Clinical Features

The hematologic manifestations are same as for cobalamin deficiency, but neurologic abnormalities do not occur. Another important difference is the time gap for deficiency to develop. Because Cbl stores are so large in in relation to daily intake, a year of inadequate intake is required before onset of symptoms occurs. On the other hand, symptoms of folate deficiency can occur within a few

weeks after intake is diminished. Older individuals who live alone and avoid cooking foods that contain folate may become deficient. Increased folate demands occur in pregnancy.

Both Cbl and folic acid are required for metabolism of homocysteine to methionine. As a result, deficiencies in these vitamins can lead to increased plasma level of homocysteine and this is a risk factor for developing atherosclerosis and venous thrombosis.

D. Diagnosis

1. Anemia
2. RBC index- MCV - >100 fl
3. Peripheral blood smear examination – macro-ovalocyte, hypersegmented neutrophil
4. Bone marrow examination- intense erythroid hyperplasia, megaloblastic change, hypercellularity of marrow
5. Serum Cbl - <200 pg/ml (N >300 pg/ml)
6. Serum folate – <4ng/ml (N 4ng/ml)
7. Specific metabolites: Serum methyl malonate level (N-0.07-0.27µmol/l) and serum homocysteine level (N 5-15 µmol/l)

a. Cbl deficiency - Both are elevated

b. Folate deficiency – only homocyteine elevated, methyl malonate (MMA) normal

4.6. Clinical Features in Common

A. Megaloblastic Anemias

1. Symptoms of anemia
2. Symptoms associated with vitamin B12 or Folic acid deficiency Neurologic manifestations (exclusivly with B12 deficiency)
3. Gastrointestinal complaints (vit.B12 and folic acid deficiency), loss of appetite glossitis (red, sore, smooth tongue), diarrhea

4.7. Investigations

A. Megaloblastic Anemias - Diagnosis

1. Blood cell count: macrocytic anemia (MCV>100fl), thrombocytopenia, leucopenia (granulocytopenia), low reticulocyte count
2. Blood smear: macro-ovalocytosis, anisocytosis, poikilocytosis, hypersegmentation of granulocytes
3. Laboratory features: indirect hyperbilirubinemia, elevation of lactate dehydrogenase (LDH), serum iron concentration- normal or increased
4. Bone marrow:
   - smear hypercellular
   - increased erythroid /myeloid ratio
   - erythroid cell changes (megaloblasts, RBC precursor - abnormally large with nuclear- cytoplasmic asynchrony)
   - myeloid cell changes (giant bands and metamyelocytes, hypersegmentation)
   - megakaryocytes are decreased and show abnormal morphology10

B. Pernicious Anemia Diagnosis

1. Establishing vit.B12 deficiency anemia
2. Absence of hydrogen ion secretion (achlorhydria) with maximal histamine stimulation
3. Radiolabeled vitamin B12 absorption test (Schilling urinary excretion test): very reduced absorption of the B12-isotope, corrected to normal only when co-administered with a source of gastric IF
4. Intrinsic factor, parietal cell and IF-vit.B12 complex antibodies13

C. Folic Acid Deficiency Anemia Diagnosis

1. Establishing megaloblastic anemia
2. History: causes of folate deficiency
3. Absence of neurologic symptoms
4. Low serum and red blood cell folic acid level

4.8. Megaloblastic Anemias Management

A. Treatment of Cobalamin Deficiency

Severe anemia is typically treated with parenteral Cbl in a dose as follows:

1000 µg (1 mg) daily x 7 days

Then 1 mg every week x 4 weeks

Followed by 1 mg every month for rest of life.

During severe anemia, iron supplementation is required because of increased utilization of iron.

B. Laboratory Monitoring

If the patient is significantly anemic, there will be a rapid reticulocytosis in 3-4 days, peaking at days 6 to 7 followed by a rise in hemoglobin and fall in MCV. Hemoglobin begins to rise within 10 days and returns to normal within 8 weeks. Hypersegmented neutrophils disappear at 10-14 days. Neurologic abnormalities improve about slowly over six months.

C. Treatment of Folate Deficiency

Folate deficiency is treated with folic acid 1-5 mg /day for 1-4 months, or until complete hematologic recovery occurs. A dose of 1 mg/day is usually sufficient.

Folic acid can partially reverse some of the hematologic abnormalities of cobalamin deficiency, but the neurologic manifestations will progress. Thus, it is important to rule out Cbl deficiency before treating a patient of megaloblastic anemia with folic acid. If

initiation of treatment is urgently required, blood samples should be obtained for appropriate assays ant the patient should be treated with both folic acid and vitamin B12 simultaneously until the results are known.

D. Indian Scenario of Megaloblastic Anemia

A study reported that 75% of selected urban population from Pune had a metabolic cause (hyperhomocsteinemia and hypermethylmalonicacidemia). Folate deficiency has been linked to poverty. In Delhi, a hospital based study showed that 2.7% of all anemia was megaloblastic anemia.

In another study from Puducherry, megaloblastic anemia was found in 38.4% out of 60 adult patients of macrocytic anemia-There was a significant male preponderance in the study, and a majoriy were young. The megaloblastic anemias observed were due to either vitamin B12 deficiency (78.3%) or combined vitamin B12 deficiency and folic acid deficiency (21.7%). None had lone folate deficiency. A significant proportion of non-vegetarians (73.9%) had megaloblastic anemia [1-5].

5. Conclusion

The pathological conditions associated with macrocytic anemia are much more diverse than is often appreciated and macrocytosis is not to be equated with megaloblastosis, since there are varied conditions associated with non-megaloblastic macrocytosis. However, the presence of macroovalocytes and hypersegmented neutrophils in peripheral smear almost always goes with a diagnosis of megaloblastic anemia. Megaloblastic anemia still remains the most important cause of macrocytic anemia in our setting. The diversity and complexity of factors leading to macrocytic anemia preclude a single or uniform method of investigation. The investigative pattern must be tailored to the individual patient, giving importance to the clinical presentation. In settings with limited laboratory facilities, a therapeutic trial of vitamin B12 or folic acid is useful in determining the specifi c vitamin defi ciency in megaloblastic anemia

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