


Megaloblastic anemia is most commonly due to deficiency of Folate or Cobalamin (vitamin B12). It is characterized by peculiar type of morphologic changes i.e. presence of megaloblasts or larger than normal sized precursors of red cells and granulocyte series in the bone marrow.

PHYSIOLOGY OF VITAMIN B12 AND FOLIC ACID

Vitamin B12

It is synthesized by micro-organisms. Higher plants and animals cannot synthesize it and must depend on external sources. Milk, vegetables, cereals, pulses, etc. are poor sources of B12. Cured, cheese, and such milk products contain B12. Contamination of legumes by B12 synthesizing bacteria is another source of B12 for a vegetarian. Non vegetarian articles of food like liver, kidney meat, oysters, crabs, egg yolk etc are rich sources of B12. B12 is synthesized by colonic bacteria but this is not available for absorption and is excreted. Fecal contamination of food and water which is responsible for infections like amebiasis etc. is ironically a source of B12 for majority of population of our country!

The daily requirement of B12 is only 1 microgram.

B12 absorption requires the presence of intrinsic factor in the gastric juice. Hydrochloric acid and enzymes are required to split B12 from its combination with proteins in food. B12 is absorbed from lower part of ileum.

Majority of B12 is stored in the liver (about 4-5 mg). Megaloblastosis occurs when the body B12 stores fall below 0.1 mg.

Folic acid

Folic acid is present in nearly all foods. Articles rich in folate are liver, yeast and green leafy vegetables. Prolonged cooking of food in large quantities of boiling water destroys folate and leads to folate-deficient diet. This is an important cause of dietary folate deficiency.

The daily requirement of folate is about 50 micrograms. Folate requirements increase in conditions with increased cell turnover for e.g. hemolytic anemias, malignancies, infections, etc.

Folic acid is absorbed from the entire length of the small intestine. Folate synthesized by the bacteria present in the colon is not absorbed.

The total body folate stores are about 5-10 mg and about one third of this is in the liver.
Deficient intake

Strictly vegetarian diet is one of the most common cause of B12 deficiency in our country, as many people follow a strict vegetarian diet due to religious beliefs.

Breast milk is a poor source of B12 and hence infants and children who are exclusively breast fed without any other supplements are also likely to develop B12 deficiency.

B12 deficiency is a common cause of anemia in older age group as they may be neglected or because of other medical problems which lead to poor oral intake.

Food fads, junk foods and lack of fresh green vegetables in the diet is the chief cause of folate deficiency. However even if vegetables are included in the diet, faulty cooking habits like excessive or over cooking of vegetables and draining the water used for cooking, make the diet deficient in folate. These practices are common in our country and so it is not uncommon to find folate deficiency in our population despite intake of good quantities of green leafy vegetables.

Impaired absorption

Intrinsic factor is necessary for B12 absorption, so conditions like pernicious anemia in which there is lack of intrinsic factor manifest with B12 deficiency. Destruction of gastric mucosa due to any cause i.e. neoplasms, atrophy, ingestion of corrosives all can lead to deficiency of intrinsic factor and thus B12 deficiency. Similarly total or partial gastrectomy would lead to decreased intrinsic factor and thus B12 deficiency. Achlorhydria and hypochlorhydria i.e. absent or decreased hydrochloric acid in the stomach impairs B12 absorption, as hydrochloric acid helps splitting B12 from its complex with proteins in food.

B12 is absorbed from ileum, hence diseases involving distal ileum like tropical sprue, celiac disease, ileal granulomas including tuberculosis, strictures, neoplasms etc lead to B12 deficiency. Ileal resection and anastomosis due to any cause also is an important cause of B12 deficiency.

Intestinal infestation by parasites especially fish tapeworm infection and even bacterial infections take up all the B12 that is taken in diet. Thus even though the intake and absorption are adequate, the patient may still suffer from B12 deficiency. Thankfully though, fish tapeworm infection is not seen in our country.

Folate absorption, like B12, is also affected by hypochlorhydria and achlorhydria as hydrochloric acid helps to liberate free folates from the conjugated form present in the food.

Similarly diseases of the small intestine like tropical sprue, celiac disease, small bowel infections and granulomas, strictures, neoplasms, diverticuli, blindloops, etc. cause folate deficiency as folate is absorbed in the small intestine. Intestinal resection, removal or bypass of long segments of small bowel also would lead to folate deficiency.

Defective utilization

Liver disease leads to defective utilization of B12 and folate. Serum B12 and folic acid levels may be high in these conditions, but their utilization is poor. Alcohol produces B12 and folate deficiency by various mechanisms such as malnutrition, gastritis leading to poor absorption and liver disease leading to impaired utilization.

Certain commonly used medications like phenytoin, pyrimethamine and methotrexate block folic acid metabolism and produce megaloblastic anemia.

Excessive requirements

Pregnancy is the most important condition leading to increased requirements of both B12 and folate. Requirements increase with multiple pregnancies and with shorter intervals between two pregnancies.

Similarly requirements are high in infancy and childhood due to rapid growth.

Conditions which cause increase in metabolism like rheumatoid arthritis also increase the demand for B12 and folate.

Increased bone marrow turnover would lead to increased requirement of B12 and folate.

Conditions like hemolytic anemias due to any cause-congenital or acquired, leukemias, myeloproliferative disorders cause increased turn over and need excess of B12 and folate.

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