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Anemia, Megaloblastic

Pronunciations: (meg′[schwa]-lo-blastic [schwa]-ne′me-[schwa)
Megaloblastic anemia is a blood disorder characterized by enlarged red blood cells, usually oval in shape (macroovalocytes), and hypersegmented nuclei in polymorphonuclear leukocytes usually resulting from either a folate or vitamin B_{12} deficiency. It has been estimated that 3.4 million Americans have some form of anemia, while the prevalence is greater in women compared to men.

Causes

Folate and vitamin B_{12} are both involved in the methylation of deoxyuridine (dUMP) to thymidine, which is essential for DNA synthesis. Defective synthesis of thymidylate, along with a large deoxyuridine triphosphate pool may lead to uracil misincorporation and cell death. Morphological changes in all blood indices (RBC's, leukocytes, platelets, and other factors) within the circulation and in bone marrow are seen, while the number of circulating cells is decreased because of enhanced apoptosis. Cell reproduction ceases in the G2 phase, preventing normal cell divison and leaving almost double the DNA present in normal cells. RNA synthesis is not impaired however, creating megaloblastic cells with normal cytomplasmic mass, but immature nuclei in the bone marrow. Megaloblastic anemia stems from six possible factors associated with folic acid or vitamin B_{12} deficiency: inadequate dietary intake, absorption, or utilization, and increased requirement, excretion, or destruction. It is important to decipher between folate and vitamin B_{12} deficiencies because each vitamin has several possible etiologies and the cause of the anemia must be discovered before administering therapy.

Vitamin B12

Pernicious anemia (lack of intrinsic factor [IF] leading to vitamin B_{12} deficiency and anemia) is often used interchangeably with vitamin B_{12} deficiency. Intrinsic factor is needed for normal B_{12} absorption, therefore, a lack of IF will cause a secondary vitamin deficiency. Although less common, vitamin B_{12} deficiency can occur from inadequate intake, as seen in strict vegans, alcoholics, and certain religious groups. In addition, malabsorption syndromes, pancreatic disease, HIV, certain drugs (eg, colchicine, metformin) and other competitive agents (eg, fish tapeworm, the blind loop syndrome) can cause a deficiency. An acquired enzyme deficiency, presence of B_{12} antagonists, hyperthyroidism, ascorbic acid in pharmacological doses, and liver disease are a few other possible factors.

Folate

Megaloblastic anemia due to folate deficiency tends to occur before a B_{12} deficiency because depletion of B_{12} stores takes several years, whereas folic acid is depleted within 2 to 4 months. The most frequent causes of folate deficiency are long-term inadequate intakes (eg, lack of green leafy vegetables, fruit juices, or excessive heating [folates are heat sensitive]), increased folate requirements (eg, infancy, Lesch-Nyhan syndrome), and impaired absorption (eg, tropical sprue) and utilization (eg, methotrexate, diphenylhydantoin and other anticonvulsants, congenital and acquired enzyme deficiencies). Alcohol interferes with the enterohepatic cycle, absorption, and utilization of folate therefore alcoholics are usually are in negative folate balance. Marginal folate intakes are common, and if coupled with excessive alcohol ingestion, can lead to a

deficiency. An increased folate requirement is evident during pregnancy and if the mother is deficient, it can significantly compromise the infant's folate status, especially if breast fed. Furthermore, a deficiency in vitamin B_{12} can result in a folic acid deficiency because B_{12} is responsible for the removal of 5-methyl to generate the metabolically active THFA. Cellular folate levels decrease (5-methyl THFA is a poor substrate for polyglutamation) because 5-methyl THFA is trapped (methylfolate trap) thereby preventing replenishment of active THFA needed for DNA synthesis and creating a buildup of homocysteine.

Diagnosis

Symptoms:

The symptoms associated with megaloblastic anemia often do not reflect the status of the disease, leading to a severe deficiency when finally detected. A deficiency in folate or vitamin B_{12} is not distinguishable when assessing a bone marrow or peripheral blood smear because hematological indices are the same. However, vitamin B_{12} deficiency can result in neurological abnormalities (eg, paresthesia, hallucinations) which are not present in folic acid deficiency. Glossitis may be an early clinical sign seen in both folate and vitamin B_{12} deficiency.

Other symptoms:

"Megaloblastic madness"
Fatigue
Dyspnea
Irritability
Intermittent diarrhea and constipation
Forgetfulness
Anorexia
Weightloss
Skin color changes
Headaches

Interpretation of Laboratory Tests

The following methods are frequently used to help reach a diagnosis for megaloblastic anemia. When diagnosing megaloblastic anemia, a blood smear assessment will show macroovalocytes, oddly shaped and uneven RBC's. A decrease in RBC's, leukocytes, and platelets will also be seen. Additional tests must be conducted in order to distinguish between a folate or vitamin B_{12} deficiency and the disease etiology.
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LABORATORY TESTS		
Test Name	Normal values	Indicators
Complete Blood Count (CBC)		MCV > 100 fL. Anemia is present; odd shaped platelets; hypersegmentation of granulocytes;

		macrocytosis.
Bone Marrow Examination		Megaloblastosis present; erythroid hyperplasia
Serum Homocysteine	5.0 - 15.0 umol/mL (0.7 - 2.0 ug/mL)	15-30 umol/mL is mildly elevated > 100 umol/mL is severely elevated
Lactate Dehydrogenase (LDH)	105 to 333 IU/L	Elevated levels may suggest hemolytic anemia

VITAMIN B12 TESTS

Test Name	Normal values	Indicators
Serum Vitamin B_{12} test	200 to 900 pg/ml	< 150 pg/mL indicates deficiency < 100 pg/ml suggests clinical deficiency (symptoms present)
Schilling Test	8% to 40% of the radioactive vitamin B12 excreted within 24 hours	Lower-than-normal absorption (< 8% with Type I Schilling test). Followed by Type II Schilling test to determine the underlying cause.
Intrinsic Factor Antibody Assay	Negative	Positive
Serum Methylmalonic Acid	0.08 to 0.56 micromoles/L	Increased in vitamin B_{12} deficiency.
Holo Transcobalamin II assay		Low levels (< 40 pg/mL [< 30 pmol/L]) may be an early sign of deficiency.
Gastric Analysis	Volume of stomach residue is 20 to 100 mL and pH is 1.5 to 3.5	Decrease in gastric secretions with a pH > 6.5

FOLATE TESTS

Test Name	Normal Values	Indicators
Serum Folic Acid test	2.7 to 17.0 ng/ml	< 4 ng/mL suggests deficiency
Red Cell Folate (RCF) levels	225 to 600 ng/mL	< 140 ng/mL suggests deficiency. Note: RCF is superior to serum folate because is measures actual body stores.
Formiminoglutamic acid (FIGLU)		Urinary measure is elevated

OTHER

Test Name	Indicators

Gastrointestinal X-rays	When pernicious anemia is present, GI x-rays may show other problems related to malabsorption. In addition, the risk for gastric cancer is elevated in these patients.
Deoxyuridine Mono-Phosphate (dUMP) Suppression Test	Test can be used to determine the cause of deficiency (folic acid vs. vitaman B_{12}). The test is mostly used for research purposes, but can be utilized in the clinical setting.

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Folic acid and vitamin B_{12} assays are prone to false-negative and false positive results, therefore a serum homocysteine and methylmalonic acid analysis are often conducted to confirm the deficient vitamin. Folic acid deficiency will present elevated homocysteine levels, but methylmalonic acid levels will be normal.[1,2] Vitamin B_{12} deficiency will show elevated homocysteine and methylmalonic acid levels.[1,2]
Pregnant women may have a low serum vitamin B_{12} status, but not be deficient. This must be taken into consideration when assessing their blood. Alcoholics on the other hand, may have normal serum folic acid levels with depleted tissue stores. It is important therefore, to complete several diagnostic tests.

Common Current Treatments

Before treatment can be administered it is crucial to determine if the anemia is a result of a folate or vitamin B_{12} deficiency. Folic acid supplementation can relieve the megaloblastic symptoms related to either vitamin. Care must be taken however, as folic acid can also mask neurological abnormalities resulting from vitamin B_{12} deficiency, which could progress to irreversible nerve damage if left untreated. Treatment of pernicious anemia is usually by injection (intramuscular or subcutaneous) of 100 µg of vitamin B_{12} once a week until status stabilizes, which is then followed by monthly injections of the same dose. Large oral doses (500 to 2000 µg/day) of vitamin B_{12} is sometimes given because diffusion (~1%) occurs with high intakes. A nasal gel is also available.
Folic acid deficiency is usually treated with a 1 mg daily oral dose for 2 to 3 weeks in order to replenish tissue folate levels. Once tissues are replenished, a daily oral dose is in the range of 50 to 100 ug/day is necessary for retention, with this requirement increasing several fold (2 to 3 times) in children and pregnant women.

Medications

Unless other problems are the cause for megaloblastic anemia, the usual treatment protocol for vitamin B_{12} or folic acid deficiency is through injection or large oral intakes of the vitamins. A vitamin B_{12} deficiency, as a result of pernicious anemia, requires life-long monthly injection (100 µg) or oral ingestion (1000 µg/day) of vitamin B_{12} once the condition has stabilized. Treatment of folic acid deficiency is usually treated with an oral intake of 1 mg/day for a few weeks, and then maintained through dietary intake.
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VITAMIN B_{12} DEFICIENCY		
Indication	Class/Examples	Notes

Lack of Intrinsic Factor (pernicious anemia) Vitamin B_{12} Deficiency	Cyanocobalamin Injection - Cyanoject - Hydroxy-Cobal Cyanocobalamin Nasal Spray Cyanocobalamin tablets or extended release (Oral)	1 mL usually contains 1000 µg Nasal spray only given if in remission, after IM injection. Normal dose is 500 µg once a week.
FOLIC ACID DEFICIENCY		
Indication	Class/Name	Notes
Folic Acid Deficiency	Folic Acid (Oral/Injection) -Vitamin B9 - Folvite	

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Once therapy has been initiated, a noticeable improvement in appetite and overall well-being will precede hematological recovery, which usually takes about one full month to recover. Reticulocyte counts should return to normal within a couple of weeks and hemoglobin concentrations will rise 20 to 30 g/L each week until reaching normal levels. If treatment is effective and then levels off, an assessment of iron should be conducted, as it may be impeding RBC production.

Dietary Interventions

It is recommended that patients recovering from a vitamin B_{12} deficiency consume a high protein diet (1.5 g/kg of bodyweight) to allow for restoration of blood and liver function. Dietary sources that are rich in vitamin B_{12} are animal sources such as liver, beef, pork, poultry, milk products, and eggs. Plant sources are usually devoid of vitamin B_{12}, unless contaminated with bacteria, thereby posing a risk for vegetarians. It is therefore recommended that vegetarians consume foods supplemented with vitamin B_{12}, or take dietary supplements.

Green leafy vegetables are excellent sources of folic acid and iron. The diet should consist of at least one fresh and uncooked vegetable, fruit, or fruit juice each day once folic acid deficiency has been resolved. Fresh fruits and vegetables are much better sources of folic acid compared to cooked sources because folic acid is destroyed during the heating process. Liver should also be consumed frequently as it is rich in folic acid, iron, and vitamin B12, however, cholesterol intake must be monitored.

What to Tell the Patient and Family

When the patient's symptoms have subsided, it is important to emphasize eating foods rich in folic acid, iron, and vitamin B_{12}. It is also important to instruct the whole family on all aspects of the diet. This applies to spouses or partners of patients.

References

1. Savage D, Lindenbaum, J. Stabler SP, and Allen RH. Sensitivity of serum methylmalonic acid and total homocysteine determinations for diagnosing cobalamin and folate deficiency. Am J Med; 1994: 96:239.

2. Allen RH, Stabler SP, Savage DG and Lindenbaum J. Diagnosis of cobalamin deficiency I: usefulness of serum methylmalonic acid and total homocysteine concentrations. Am J Heme; 1990: 34:90.

