Pernicious anemia (PA) is an autoimmune disorder that causes neurological changes, including dementia, and a condition of anemia related to vitamin B12 deficiency.

Vitamin B12

Vitamin B12 is an essential nutrient derived from dietary animal protein such as meat, poultry, fish, cheese, eggs and fortified cereals. Vitamin B12 is absorbed in the gastrointestinal track in the presence of gastric hydrochloric acid and pepsinogen when *intrinsic factor*, a protein secreted by the parietal cells lining the stomach, binds vitamin B12 as it passes through the small intestine. Even without intrinsic factor, a small amount of vitamin B12 from food or supplements can diffuse passively through the ileum during digestion.

Pernicious Anemia

Pernicious anemia (PA) is an autoimmune condition of anemia caused by a deficiency of vitamin B12. Vitamin B12 deficiency can have many causes including PA, malabsorption syndromes, and food cobalmin deficiency. In PA, an autoimmune process that inactivates intrinsic factor or damages parietal cells or their proton pumps leads to the disease process. Vitamin B12 deficiency in PA occurs when autoantibodies to intrinsic factor or parietal cells reduce levels of intrinsic factor by interfering with its absorption.

Symptoms and Diagnostic Problems

Similar to conditions of gastric mucosal atrophy, in PA diminished amounts of intrinsic factor can cause neurological aberrations before signs of anemia develop. PA doesn't necessarily cause anemia, but it leads to anemia when gastritis (gastrointestinal inflammation) and lack of intrinsic factor prevent intestinal absorption of vitamin B12.

Further complicating diagnosis, the deficiency of vitamin B12 is masked when large doses of folic acid (folate) are administered. In this situation there is a lack of the amino acid methionine, which is necessary for neurological health, but there is sufficient folate for red blood cell production. Neurological problems caused by vitamin B12 deficiency may not be identified. Because many foods today are fortified with folate anemia may not be evident even with low vitamin B12 levels. When anemia becomes overt, the mean corpuscular volume (MCV) of the red blood cell is typically increased, generally to levels higher than 108.

Megaloblastic Anemia
Historically, vitamin B12 deficiency was recognized as a megaloblastic form of anemia that progresses to a neurological condition. Today, it's known that neurological changes can occur in vitamin B12 deficiency even in the absence of anemia, particularly when folic acid levels are high. Vitamin B12 deficiency can lead to a type of dementia very similar to that seen in Alzheimer's disease. And relying on an elevated MCV as a diagnostic marker puts patients at risk of not being diagnosed.

**Red Blood Cell Indices**

Although changes in red blood cell indices offer valuable clues, more specific diagnostic tests are used today to diagnose vitamin B12 deficiencies and conditions of pernicious anemia. In patients with concurrent conditions of iron deficiency and PA, for instance, the MCV, which is usually elevated in B12 deficiency and low in iron deficiency, will be normal. Another hematological change, the appearance of hypersegmented polymorphonuclear white blood cells, is seen in vitamin B12 deficiency. However these cells are also present in other conditions, diminishing its value as a diagnostic tool. The Schilling test, which was once the best method for diagnosing pernicious anemia, is now considered obsolete.

**Diagnosis**

Today, the best tests for diagnosing pernicious anemia are the vitamin B12 level, folic acid level, methylmalonic (MMA) level, and antibody tests for antibodies to intrinsic factor and parietal cells. Levels of MMA are elevated in both serum and urine before levels of vitamin B12 become abnormally decreased or symptoms of deficiency appear. The blood test for MMA is considered superior to the urine measurement.

The serum homocysteine level is also a good indicator of vitamin B12 deficiency because of the inability of homocysteine to produce methionine when B12 levels are low. In vitamin B12 deficiency states, the homocysteine level is elevated. Tests for holo-transcobalamin II (Holo-TC II) are also used to determine the amount of vitamin B12 that is directly available to cells. A low result is an early, sensitive marker of vitamin B12 deficiency. Tests for serum gastrin and pepsinogen are also used to help diagnose PA. In pernicious anemia, low levels of stomach acid stimulate gastrin production and gastrin levels are elevated. Low total pepsinogen levels or low levels of pepsinogen I compared to pepsinogen II are seen in PA.

Antibodies to intrinsic factor may be either binding or blocking antibodies. Binding antibodies bind to the intrinsic factor binding site and interfere with the absorption of intrinsic factor. Blocking antibodies bind to the receptor of cells in the ileum preventing intrinsic factor absorption. Although only some patients with pernicious anemia have intrinsic factor antibodies, all patients with intrinsic factor antibodies have PA. These antibodies, which are more likely to occur in black and Latin American patients than white patients, have a greater specificity for PA. More patients with PA have parietal cell antibodies, but these antibodies are seen in other autoimmune conditions such as atrophic
gastritis. For this reason, antibodies to intrinsic factor are considered superior for diagnosing PA.

**Patients with Graves’ Disease**

PA and atrophic gastritis are the two most common autoimmune disorders to develop in patients with Graves' disease, especially in patients with ongoing immune stimulation, including Graves' disease patients who have had radioiodine ablation.

**Resource:**

Majid Moidani and Shana Ben-Poorat, Laboratory Investigation of Vitamin B12 Deficiency, Laboratory Medicine, March 2006.

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