Pernicious Anaemia and B12 Deficiency

Vitamin B12 is present in meat and animal protein foods. Absorption occurs in the terminal ileum and requires intrinsic factor (IF), a secretion of gastric mucosal (parietal) cells, for transport across the intestinal mucosa. In pernicious anaemia, IF production is deficient. It is believed to be an autoimmune disease.

*Helicobacter pylori* infection has been mooted to be an initiating factor, with subsequent autoimmune changes affecting the gastric mucosa. Genetic susceptibility to this process has been suspected.

Causes[2]

Pernicious anaemia accounts for 80% of cases of megaloblastic anaemia due to impaired absorption of vitamin B12. Other causes of vitamin B12 deficiency include:

- Gastric causes: gastrectomy, gastric resection, atrophic gastritis, *H. pylori* infection or congenital IF deficiency or abnormality.
- Inadequate dietary intake of vitamin B12 - eg, a vegan diet.
- Intestinal causes - eg, malabsorption, ileal resection, *Crohn's disease* affecting the ileum, *chronic tropical sprue*, HIV and any radiotherapy causing irradiation of the ileum.
- Drugs - eg, colchicine, neomycin, metformin, anticonvulsants.
- Long-term use of drugs that affect gastric acid production (eg, H2 receptor antagonists, proton pump inhibitors) can worsen deficiency because gastric acid is needed to release vitamin B12 bound to proteins in food.

Epidemiology[2]

- The incidence of pernicious anaemia is 1:10,000 in northern Europe.
- The disease occurs in all races. The peak age is 60, although it is starting to be recognised in younger age groups.[3]
- The condition is more common in those with blue eyes, early greying, a positive family history and blood group A. The condition has a female: male ratio of 1.6:1.0.

Presentation[2]

Symptoms of anaemia may include fatigue and lethargy, dyspnoea, faintness, palpitations and headache. Vitamin B12 deficiency may present with unexplained neurological symptoms - eg, paraesthesia, numbness, cognitive changes or visual disturbance.

Findings on examination may include pallor, heart failure (if anaemia is severe), lemon tinge to the skin, glossitis and oral ulceration. Neuropsychiatric features may include irritability, depression, psychosis and dementia. Neurological features may include subacute combined degeneration of the spinal cord and peripheral neuropathy.

- Peripheral loss of vibratory sense and position are early indications of central nervous system (CNS) involvement, accompanied by reflex loss and mild-to-moderate weakness. Later stages may be characterised by spasticity, Babinski's responses and ataxia.
- Other uncommon neurological symptoms include impairment of pain, temperature and touch sensations. The legs and feet are involved earlier and more consistently than the hands.
- Yellow-blue blindness may occur.
- Psychiatric symptoms (usually more prominent in advanced cases) may include depression, paranoia (megaloblastic madness), delirium, confusion and dementia.
- Severely anaemic patients may present with heart failure, often triggered by an infection. Hepatomegaly and splenomegaly may be present.
Differential diagnosis

Causes of megaloblastic anaemia

- **Folate deficiency** - poor diet, goat's milk, gluten-induced enteropathy, tropical sprue, pregnancy, prematurity, chronic haemolytic anaemias (eg, sickle cell anaemia), malignant disease, increased renal loss (congestive cardiac failure, dialysis), drugs (anticonvulsants, sulfasalazine).
- Functional vitamin B12 deficiency: neurological complications such as subacute combined degeneration of the spinal cord may occur despite normal serum B12 levels. Failure of intracellular transport of B12 by transcobalamin-2 can lead to functional B12 deficiency but with apparently normal serum levels.

Causes of macrocytosis

- Alcohol excess.
- Liver disease.
- Severe hypothyroidism.
- Reticulocytosis (eg, post-acute blood loss or haemolytic anaemia).
- Other blood disorders - red-cell aplasia, aplastic anaemia, myeloid leukaemia, myelodysplastic disorders.
- Changes in plasma proteins (eg, increased paraprotein secondary to multiple myeloma) may cause a spurious rise in mean cell volume (MCV) without the presence of macrocytes.
- Drugs that affect DNA synthesis - eg, azathioprine, hydroxyurea.

Investigations

**FBC**

- This may show low haemoglobin and increased MCV, although macrocytosis can precede the development of anaemia. Severe cases may show a pancytopenia.
- The reticulocyte count may be low for the degree of anaemia (1-3% only).
- The MCV may be normal if there is associated iron deficiency.

**The blood film**

- This may show macrocytic red cells, neutrophils with hypersegmented nuclei and Howell-Jolly bodies (residual fragments of the nucleus causing spherical blue-black inclusions on red blood cells) seen on Wright-stained smears.
- Associated iron deficiency may result in the MCV being normal, in which case two types or red blood cells may be seen (a dimorphic blood film).
- The ferritin level should be checked if such a picture is seen.

**Biochemistry**

- There may be an increase in plasma unconjugated bilirubin due to increased destruction of red cell precursors in the marrow. LFTs, TFTs and protein electrophoresis may help in the differential diagnosis of macrocytosis.
- Serum vitamin B12 is the most commonly used method of establishing B12 deficiency. In general, levels <111 pmol/mL reliably indicate deficiency. Neurological deficiency or anaemia is usually evident in patients with levels <89 pmol/mL. False positives (low levels in the absence of deficiency) can occur with pregnancy, folate deficiency, myeloma, and excessive vitamin C intake.
- False negatives (normal levels in the presence of deficiency) may occur in true deficiency, liver disease, lymphoma, autoimmune disease and myeloproliferative disorders. In borderline cases or where B12 deficiency is clinically suspected, other tests must be carried out. Tissue deficiency of B12 results in raised levels of serum methylmalonic acid and this is a useful test where false positive of negative values are suspected. Other tests include transcobalamin II B12 content and plasma total homocysteine.
Folic acid levels should be measured to exclude deficiency, which may co-exist with B12 deficiency. Red cell folate is a better guide to deficiency than serum folate. B12 deficiency may result in increased serum folate levels but reduced red cell folate levels, because of the effect on intracellular folate metabolism. Combined deficiency usually results in both reduced serum folate and vitamin B12 levels.

**Autoantibody screen**

IF antibodies (IFAs), if present, are virtually diagnostic (100% specific) for pernicious anaemia. However IF antibodies have lower sensitivity with studies showing IFAs present in as few as 27% of patients. Therefore the absence of IFAs does not rule out the diagnosis of pernicious anaemia.

Gastric parietal cell antibodies (PCAs) are less specific but more sensitive for pernicious anaemia. Combining IFA's and GCA's increases the sensitivity to 73% while maintaining 100% specificity for pernicious anaemia.

**Schilling test**

The test measures the absorption of B12 by assessing increased urine radioactivity after an oral dose of radioactive B12. This test is now rarely used.

**Bone marrow aspiration**

This may be necessary to narrow the differential diagnosis, especially if myelodysplasia, aplastic anaemia, myeloma, or other marrow disorders are suspected. In B12 and folate deficiency, megaloblasts and giant metamyelocytes (early granulocyte precursors) are seen.

**Gastric secretions**

Total gastric secretions are reduced to approximately 10% of the reference range; most patients have achlorhydria and absent intrinsic factor.

**Gastroscopy**

This is appropriate on diagnosis to confirm gastric atrophy and exclude gastric cancer and polyps. Gastric cancer is two to three times more common in patients with pernicious anaemia than in matched controls.

**Associated diseases**

People with pernicious anaemia are at increased risk of developing gastric cancer, and there is an association with other autoimmune diseases (including primary myxoedema, thyrotoxicosis, Hashimoto's disease, Addison's disease, and vitiligo).

- Vitiligo
- Primary hypothyroidism
- Hashimoto's disease
- Addison's disease
- Hypoparathyroidism
- Diabetes mellitus

**Management**

- For patients with no neurological involvement, treatment is with six injections of hydroxocobalamin, 1 mg in 1 mL at intervals of between 2-4 days.
- Subsequently, 1 mg is usually given at intervals of three months. There is as yet no evidence-based guidance as to the optimum regime but the National Institute for Health and Care Excellence (NICE) is considering releasing guidance in due course. It should be remembered that serum B12 is not always an accurate reflection of deficiency at a cellular level. It is perhaps for this reason that some patients become symptomatic if the frequency of their injections is reduced, despite having normal serum B12 levels.
- For patients with neurological involvement, referral to a haematologist is recommended. Initial treatment is with hydroxocobalamin 1 mg on alternate days until there is no further improvement, after which 1 mg should be given every two months for life.
• Care should be taken not to give folic acid (instead of B12) to any patient who is B12-deprived, as this may result in fulminant neurological deficit.
• Oral iron therapy should be given before B12 if iron deficiency is diagnosed by an absence of stainable Fe in the bone marrow or other parameters (eg, serum ferritin <449 pmol/mL).

When to refer
Referral to a gastroenterologist should be considered for any patient with pernicious anaemia who has gastric symptoms and/or co-existent iron deficiency. Patients with pernicious anaemia have a 2-3 times increased incidence of gastric carcinoma and gastric polyps compared with matched controls.

Complications
• Heart failure - this may be secondary to anaemia, or rarely, myocarditis.
• Angina.
• Neuropathy - subacute combined degeneration of the cord, optic atrophy, neurosis, depression and dementia.
• Gastric carcinoma.[12]
• Infertility (rare).
• Iron-deficiency anaemia - secondary to the achlorhydria which results from gastric mucosa atrophy.
• People with pernicious anaemia are at increased risk of developing gastric cancer.

Prognosis
Before the advent of treatment with B12, the disease was fatal. Hence the name 'pernicious'. However, pernicious anaemia responds rapidly to replacement therapy and most patients have a normal lifespan with little morbidity. If the deficiency has been severe and prolonged, any neurological complications may be irreversible.[2]

Further reading & references

• Guidelines for the diagnosis and treatment of Cobalamin and Folate disorders; British Committee for Standards in Haematology (2014)

2. Anaemia - B12 and folate deficiency; NICE CKS, February 2013
5. Howell-Jolly Bodies; Clinical Chemistry and Hematology Wadsworth Centre
6. Red blood cell morphology; Faculty of Health Sciences, Stellenbosch University, 2010
11. Hematopathology; Pictures of giant metamyelocytes

Disclaimer: This article is for information only and should not be used for the diagnosis or treatment of medical conditions. EMIS has used all reasonable care in compiling the information but make no warranty as to its accuracy. Consult a doctor or other health care professional for diagnosis and treatment of medical conditions. For details see our conditions.
Ask your doctor about Patient Access

- Book appointments
- Order repeat prescriptions
- View your medical record
- Create a personal health record (iOS only)

Simple, quick and convenient.
Visit patient.info/patient-access or search 'Patient Access'

© EMIS Group plc - all rights reserved.