Macrocytosis and macrocytic anaemia

Definition

Macrocytosis means that the red blood cells are larger than normal. Macrocytic anaemia occurs when there is also a fall in haemoglobin levels in the blood. Anaemia is usually defined as a haemoglobin level of at least two standard deviations below the mean for that age and sex. By this definition, 2.5% of a normal population will be classified as anaemic.The figures are usually taken as below 13 g/dL for men and below 12 g/dL for women. Children have a lower haemoglobin than adults.

As a general rule, macrocytosis occurs when there are problems with the synthesis of the blood cells, as in vitamin B12 or folic acid deficiency, whilst microcytosis is associated with deficiency of haemoglobin production, such as iron deficiency or thalassaemia. New cells, especially reticulocytes, are also slightly larger and so, if they occur in excessive numbers, there may be macrocytosis.

Pathogenesis

The term macrocytosis describes the presence of macrocytes on a blood film, together with a raised mean corpuscular volume (MCV). It is a common finding in the results of an FBC and may or may not be associated with an anaemia. Macrocytosis may occur as a laboratory artefact, perhaps following incorrect storage of the sample. A spuriously raised MCV may also occur due to cold agglutinins, paraproteins as in myeloma, hyperglycaemia or marked leukocytosis. Macrocytic anaemia describes a macrocytosis associated with a reduced haemoglobin and most commonly occurs as a result of a megaloblastic anaemia.

Macrocytic anaemia can be classified as megaloblastic and non-megaloblastic. Megaloblastic refers to a characteristic abnormality of the erythroblasts in the bone marrow in which the maturation of the nucleus is delayed relative to the cytoplasm. It results from defective DNA synthesis.

In patients with liver disease and obstructive jaundice, cholesterol and/or phospholipids become deposited on the membranes of circulating red blood cells, leading to larger than normal cells .

Epidemiology[1]

- One study found that the most common cause of macrocytosis was medication (37%), followed by alcoholism (26%). Serum B12 and/or folate deficiency, bone marrow dysplasia and non-alcoholic liver disease each accounted for 6%[2] .
- The most common cause of megaloblastic anaemia is pernicious anaemia. The peak age of diagnosis is 60 years with a female-to-male ratio of 1.6:1. There is often a family history and it may be associated with other autoimmune disorders.
- Vitamin B12 deficiency or folic acid deficiency together account for most cases of megaloblastic anaemia.
- Vitamin B12 deficiency can be due to disease of the terminal ileum (especially Crohn's disease) and other rare causes.

Causes of megaloblastic anaemia

The liver has abundant stores of vitamin B12 and so, if absorption is impaired, it takes 4 or 5 years for deficiency to develop.

- Vitamin B12 deficiency due to:
    - Autoimmune Addisonian pernicious anaemia (80%).
    - Potential after-effects of surgery - eg, gastrectomy or ileal resection.
    - Bacterial overgrowth or parasitic infestation.
    - HIV infection.
    - Dietary deficiency, which may occur in strict vegans but, even in them, it is rare.
    - Pernicious anaemia.
- Folate deficiency due to:
    - Dietary deficiency.
    - Malabsorption.
    - Increased demands including haemolysis, leukaemia and rapid cell turnover as may occur in some skin diseases. Macrocytosis but without anaemia will develop in 30% of women in late pregnancy unless they take folic acid supplements.
    - Increased urinary excretion occurs in heart failure, acute hepatitis and dialysis.
    - Drug-induced deficiency includes alcohol, anticonvulsants, methotrexate, sulfasalazine and trimethoprim but only if high-dose and a prolonged course.

Causes of non-megaloblastic macrocytosis

- Alcohol abuse is a common cause. There may also be folate deficiency due to a poor diet although beer is a good source of folate.
- Liver disease.
- Severe hypothyroidism.
- Reticulocytosis.

- Other blood disorders including aplastic anaemia, red-cell aplasia, myelodysplastic syndromes, myeloid leukaemia.
- Drugs that affect DNA synthesis, such as azathioprine.

Presentation

Macrocytosis per se does not cause any symptoms or signs but there may be features related to the underlying disease. Mild anaemia may be asymptomatic. Most cases are diagnosed when a blood count is performed as part of an investigation for something other than features of anaemia. People who are older or have coronary heart disease are more likely to have symptoms, whilst the young can be remarkably anaemic and not complain.

Symptoms may include:

- Shortness of breath on exertion.
- Fatigue.
- Palpitations.
- Exacerbation of angina.
- Complaining of looking pale.

Overt high-output cardiac failure can occur. Physical signs also depend upon the degree of anaemia and may include:

- Pallor. Look at the nail beds and tongue.
- A bounding pulse.
- Systolic pulmonary flow murmur.

The term **pernicious anaemia** emphasises that onset is slow and gradual. There are three classic diseases in which the doctor who has known the patient well over the years is at a disadvantage, whilst the new doctor may instantly recognise a 'barn door' diagnosis. They are pernicious anaemia, myxoedema and acromegaly.

Differential diagnosis

Megaloblastic anaemia is not a final diagnosis and a cause for the condition must be sought.

Investigations[1] [3]

- The first investigation is FBC with examination of a blood film.
- A raised reticulocyte count may indicate rapid turnover of erythrocytes.
- Serum folate levels are readily available but most laboratories offer red cell folate that is more specific.
- Serum vitamin B12 level.
- Abnormal LFTs may suggest alcohol abuse or other diseases.
- As a matter of routine, perform urinalysis, U&E and creatinine. This is because of the association with diabetes and homocystinuria. Homocystinuria can cause haematuria, proteinuria, and mild uraemia.
- A Coombs' test may be required to exclude haemolytic anaemia.
- Usually bone-marrow examination is not necessary unless an underlying haematological disease such as leukaemia is suspected.
- Perform other tests as may be required from clinical suspicion.

Associated diseases

- Pernicious anaemia is commonly found in association with other autoimmune diseases, such as diabetes and hypothyroidism and patients diagnosed as having pernicious anaemia should be screened for these routinely, both at diagnosis and at annual review.
- Vitamin B12 deficiency can also be associated with neurological features but they will not be considered here.
- There is a three-fold increase in the risk of gastric carcinoma, raising it to 4%.

- Folate deficiency in early pregnancy may be associated with neural tube defects.
- Defects in vitamin B12 metabolism can be associated with homocystinuria.

Management[1]

Management involves two components:

- Correcting the deficiency that has caused the macrocytosis, with or without anaemia.
- Treating the underlying condition that led to the deficiency.

Vitamin B12 is ubiquitous in food and so deficiency is usually due to malabsorption. Hydroxocobalamin is usually given by parenteral injection in the form of 1 mg in 1 mL. In severe anaemia it may need to be given every week at first but before long this is changed to once every three months and continued for life. There is as yet no evidence-based guidance as to the optimum regime.

Serum B12 is not always an accurate reflection of deficiency at a cellular level. Functional vitamin B12 deficiency (with normal serum B12) is common in the elderly and is associated with neurocognitive abnormalities, but its cause is unknown[4] .

The use of oral and nasal cobalamin is being researched and may be of value in mild B12 deficiency, particularly in the elderly. Neither preparation is currently available in the UK[5] .

Folic acid is produced in 5 mg tablets. The oral form is usually sufficient, although in severe malabsorption it may be necessary to give it parenterally. The usual dose is 5 mg daily for four months after which a tablet is given between one and seven days a week, depending upon the nature of the malabsorption.

If there is both folate and vitamin B12 deficiency, it is essential to start treating the B12 deficiency before starting folate, or the latter may aggravate the B12 deficiency and precipitate subacute combined degeneration of the cord.

As well as treating the deficiency, attention must be paid to the underlying condition. With pernicious anaemia, this usually involves just injections every three months, an annual FBC and a great readiness to investigate any suspicion of gastric malignancy.

Alcoholism diagnosis and management in primary care can be very difficult, not least because of the problem of denial.

When to refer

It is important to consider when specialist help should be sought.

Refer to a haematologist

- Urgently if:
  - There are neurological symptoms.
  - The patient is pregnant.
  - The suspected cause is haematological malignancy.
- Routinely if:
  - The cause of vitamin B12 or folate deficiency is uncertain following investigations, or other blood disorder is suspected.

Refer to a gastroenterologist

- If there is suspected malabsorption of vitamin B12 (other than pernicious anaemia) or folate.
- If the person has pernicious anaemia and gastrointestinal symptoms.
- Urgently if there is a suspicion of gastric cancer (eg, because of co-existing iron deficiency).
- If the patient is folate-deficient and antibody testing suggests coeliac disease (positive for anti-endomysial or anti-transglutaminase antibodies).

The urgency of referral will depend on the nature of the symptoms.

Consider referral to a dietician

- If vitamin B12 or folate deficiency is thought to be due to a poor diet.

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Originally Published: 20/11/2023	Next review date: 24/08/2020	Document ID: doc_2411

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