Macrocytosis and macrocytic anaemias

Background information

Patient information

Updates to this pathway

Macrocytosis: MCV > 100fl

Potential causes

Is the patient anaemic?

Macrocytosis without anaemia

Macrocytosis with anaemia

Examine blood film report

Examine blood film report

Consider further investigations

Consider further investigations

Investigation results

Chronic liver disease suspected

Folate low: consider aetiology

Serum vitamin B12 low/borderline

Hypothyroidism detected

Further investigations normal?

Go to abnormal liver tests

Management

Investigate cause

Treat with levothyroxine

Consider referral to clinical haematology

Follow-up

Follow-up

Follow-up

Management

Follow-up

Go to abnormal liver tests
1 Background information

Quick info:
Scope:
• diagnosis and management of macrocytosis and macrocytic anaemia in adults
Out of scope:
• other types of anaemia (see iron deficiency anaemia and Haemolytic anaemia
• use of folate supplementation for other indications
Definition:
• macrocytosis refers to a raised mean cell volume resulting from enlarged erythrocytes
• macrocytosis can exist alone or with anaemia. Macrocytosis without anaemia is often due to causes other than vitamin B12 and folate deficiency
• vitamin B12 or folate deficiency is the most common cause of megaloblastic anaemia (a type of macrocytosis in which DNA synthesis is impaired):
• pernicious anaemia is the most common cause of vitamin B12 deficiency
Incidence:
• pernicious anaemia has an incidence of 1:10,000 in Northern Europe
• prevalence of vitamin B12 or folate deficiency has been reported as approximately 5% in those between age 65-74 years and more than 10% in those age 75 years or older
• of those with vitamin B12 deficiency, approximately 10% also had low folate levels
Risk factors/aetiology for folate deficiency:
• inadequate dietary intake, eg due to alcoholism
• poor absorption, eg due to:
  • coeliac disease
  • inflammatory bowel disease
  • certain drugs, eg colestyramine, sulfasalazine, methotrexate
• periods of increased demand, eg:
  • pregnancy
  • prematurity and infancy
  • malignancy, eg leukaemia
  • inflammation, eg Crohn's disease, malaria
  • blood disorders, eg haemolytic anaemia
• excessive urinary excretion
• anticonvulsants
Risk factors/aetiology for vitamin B12 deficiency:
• most common is pernicious anaemia (impaired absorption of vitamin B12 due to lack of intrinsic factor [IF]) – pernicious anaemia is often familial (30% of cases have a family history)
• rare:
  • gastrectomy
  • gastric bypass surgery
  • gastric stapling
  • ileal resection
  • autoimmune disorders, eg Crohn's disease
  • HIV
  • inadequate dietary intake, eg due to veganism

2 Patient information
Macrocytosis and macrocytic anaemias

Quick info:
http://www.patient.co.uk/doctor/Macrocytosis-and-Macrocytic-Anaemia.htm

http://www.patient.co.uk/health/Anaemia-(Pernicious)-and-Vitamin-B12-Deficiency.htm

http://www.patient.co.uk/health/Folic-Acid-Deficiency-Anaemia.htm

3 Updates to this pathway

Quick info:
This pathway has been locally developed for South West Hampshire.
Contributors to this pathway:
• Dr Jason Mainwearing, SUHT
• Ms Julia Bowey, NHSSC

4 Macrocytosis: MCV > 100fl

Quick info:
At SUHT, a macrocytosis is an MCV of > 100 fl.
• the probability of vitamin B12 or folate deficiency increases as the MCV rises, and especially if MCV >130fl
• patients receiving hydroxycarbamide usually have MCV >110fl and do not need further testing
• MCV 100-110fl are more likely to be related to causes other than vitamin B12 or folate deficiency

5 Potential causes

Quick info:
The more common causes of macrocytosis are:
• effects of alcohol or liver disease
• B12 or folate deficiency
• the following drugs can worsen, but not cause, vitamin B12 deficiency:
  • anti-epileptics
  • neomycin
  • metformin
  • proton pump inhibitors (PPIs)
  • H₂ receptor antagonists
  • colchicine
• drugs such as methotrexate, azathioprine and hydroxycarbamide
• haemolytic disorders
• hypothyroidism
• paraproteins
• myelodysplasia
An isolated macrocytosis also occurs with cigarette smoking.

6 Is the patient anaemic?

Quick info:
At SUHT, anaemia is defined as:
• Hb < 120 g/l for a woman
9 Examine blood film report

Quick info:
Blood film:
- hypogranular neutrophils/no hypersegmented neutrophils suggest myelodysplasia
- hypersegmented neutrophils and macro-ovalocytes associated with vitamin B12 and folate deficiency
- uniform macrocytosis, often with stomatocytes, associated with alcohol abuse
- target cells associated with liver disease
- polychromasia associated with haemolysis

10 Examine blood film report

Quick info:
Blood film:
- hypogranular neutrophils/no hypersegmented neutrophils suggest myelodysplasia
- hypersegmented neutrophils and macro-ovalocytes associated with vitamin B12 and folate deficiency
- uniform macrocytosis, often with stomatocytes, associated with alcohol abuse
- target cells associated with liver disease

11 Consider further investigations

Quick info:
Further possible investigations should be based on blood film report and presence/absence of anaemia.
In the absence of anaemia, or changes on the blood film consistent with vitamin B12 or folate deficiency, then consider the following investigations initially:
- smoking and alcohol history
- if taking methotrexate, azathioprine or hydroxycarbamide, no further investigations required in the absence of anaemia
- liver function tests and Gamma GT
- thyroid function tests
- serum vitamin B12 and serum folate assays
  - especially if malabsorption, severe oropharyngeal ulceration, neuropsychiatric abnormalities such as paraesthesia, ataxia, peripheral neuropathy or memory loss

12 Consider further investigations

Quick info:
Further possible investigations should be guided by the blood film, but may include:
- reticulocyte count (raised in haemolysis or active bleeding)
- LDH (raised in haemolysis)
- serum vitamin B12 and serum folate assays
  - especially if malabsorption, severe oropharyngeal ulceration, neuropsychiatric abnormalities such as paraesthesia, ataxia, peripheral neuropathy or memory loss
- liver function tests and Gamma GT
- thyroid function tests
14 Hypothyroidism detected

Quick info:
Biochemical hypothyroidism is characterised by:
- thyroid stimulating hormone (TSH) levels greater than 10 mU/L with free thyroxine (FT4) levels low or normal; or
- TSH above normal but less than 10 mU/L with normal FT4 in presence of unexplained symptoms consistent with hypothyroidism, or if planning pregnancy

16 Serum vitamin B12 low/borderline

Quick info:
- serum vitamin B 12 less than 160ng/L indicates deficiency
- if vitamin B12 is low normal (160-180ng/L) then deficiency cannot be excluded, and repeat measurement 3 months later
If there is co-existent folate and vitamin B12 deficiency, vitamin B 12 should be replaced before folate. Administration of folate in B12 deficient patients can precipitate acute combined degeneration of the cord.

17 Folate low: consider aetiology

Quick info:
Drugs:
- phenytoin
- trimethoprim
- methotrexate
Poor diet:
- alcohol excess
- green vegetables and liver contain folate
Malabsorption:
- look for low calcium (reduced vitamin D absorption) and low iron
- coeliac disease (ferritin and tissue transglutaminase)
- consider OGD
Increased utilisation:
- malignancy
- pregnancy or lactation
- psoriasis
- chronic inflammation (consider vasculitis)

18 Further investigations normal?

Quick info:
If the above investigations are normal, check:
- plasma protein electrophoresis looking for a paraprotein
If no abnormality is identified, then myelodysplasia is a possibility. Either discuss with a haematologist or refer to the general haematology clinic if the patient has a symptomatic anaemia.

Local administrative info:
Classification of anaemias
SUHT consultants:
- Dr Andrew Duncombe: 02380 796164
- Dr Syed Kazmi: 02380 798862
19 Investigate cause

Quick info:

- pernicious anaemia (impaired absorption of vitamin B12 due to lack of intrinsic factor [IF]) is the most common cause – pernicious anaemia is often familial (30% of cases have a family history)
- other (rare) causes or contributing factors include:
  - gastrectomy
  - gastric bypass surgery
  - gastric stapling
  - ileal resection
  - autoimmune disorders, eg Crohn’s disease
  - HIV
  - Medications that interfere with gastric acid production and can cause reduced absorption of B12 from ingested protein in food eg. long term PPIs.
  - inadequate dietary intake, eg due to veganism
- Check serum anti-intrinsic factor antibody:
  - highly specific for pernicious anaemia, but low sensitivity (50%)
  - if anti-intrinsic factor antibody is present, pernicious anaemia is very likely, but its absence does not rule out pernicious anaemia
- Check anti-parietal cell antibody:
  - sensitivity of anti-parietal cell antibody for pernicious anaemia is more than 90% – however, specificity is only 50%
  - in the absence of anti-parietal cell antibody it is unlikely that the person has pernicious anaemia

20 Treat with levothyroxine

Quick info:

- initial dose of levothyroxine usually 50-100 micrograms daily, depending on body weight
- adjust dosage by 25-50 microgram increments
- initial dose 25 micrograms daily if >50 years (especially those with ischaemic heart disease) and change dose by smaller increments (eg 25 micrograms daily)
- measure serum thyroid stimulating hormone (TSH) concentration after 6 weeks and titrate dose if needed
- correct dose is that which restores the euthyroid state and relieves symptoms
- dose of thyroxine aims to achieve TSH within lower half of the reference range

22 Management

Quick info:

Published: 19-May-2011   Valid until: 19-May-2012   Printed on: 01-Aug-2011   © Map of Medicine Ltd

This care map was published by Southampton Area. A printed version of this document is not controlled so may not be up-to-date with the latest clinical information.
**Macrocytosis and macrocytic anaemias**

**Medicine > Haematology and haemostasis > Macrocytosis and macrocytic anaemias**

Give folic acid 5mg once daily for 4 months:
- ensure there is no co-existent vitamin B12 deficiency - in such individuals, vitamin B 12 should be replaced before folate administration of folate in B12 deficient patients can precipitate acute combined degeneration of the cord

23 Follow-up

Quick info:
Review after 4 months, with full blood count.
If cause of folate deficiency has been addressed, stop treatment. Otherwise, consider long term treatment

24 Management

Quick info:
Consider seeking specialist advice in pregnancy or if there are neurological symptoms.
Initial treatment:
- intramuscular (IM) injections of hydroxocobalamin on alternate days for 2 weeks

Long-term treatment where the underlying cause is not dietary:
- IM injections of hydroxocobalamin every 3 months for life

Long-term treatment where the underlying cause is dietary:
- advise either:
  - oral cyanocobalamin tablets daily between meals (available as a food supplement, and only prescribable on FP10 under special circumstances with 'SLS' endorsement required- see BNF); or
  - twice-yearly hydroxocobalamin injection (may be preferable in the elderly who are more likely to have malabsorption)
  - in vegans, this treatment may need to be life-long
  - in non-vegans treatment can be stopped once vitamin B12 levels have been corrected and diet has improved
- advise consumption of foods rich in vitamin B12, eg:
  - foods fortified with vitamin B12 – some soy products, and some breakfast cereals and breads
  - meat, eggs, and dairy products

25 Follow-up

Quick info:
Full blood count (FBC) and reticulocyte count should be performed after 10 days to check response to treatment:
- there should be a rise in the haemoglobin level and an increase in the reticulocyte count to above normal range
- if there is no improvement, check serum folate level (if this has not already been done)

FBC after 8 weeks to confirm normal blood count
Further monitoring is generally considered unnecessary – exceptions to this are:
- suspected lack of compliance with treatment
- suspected recurrence of anaemia
Macrocytosis and macrocytic anaemias

Key Dates
Published: 19-May-2011, by Southampton Area
Valid until: 19-May-2012