Lecture_4

Megaloblastic anaemia

Fifth year students

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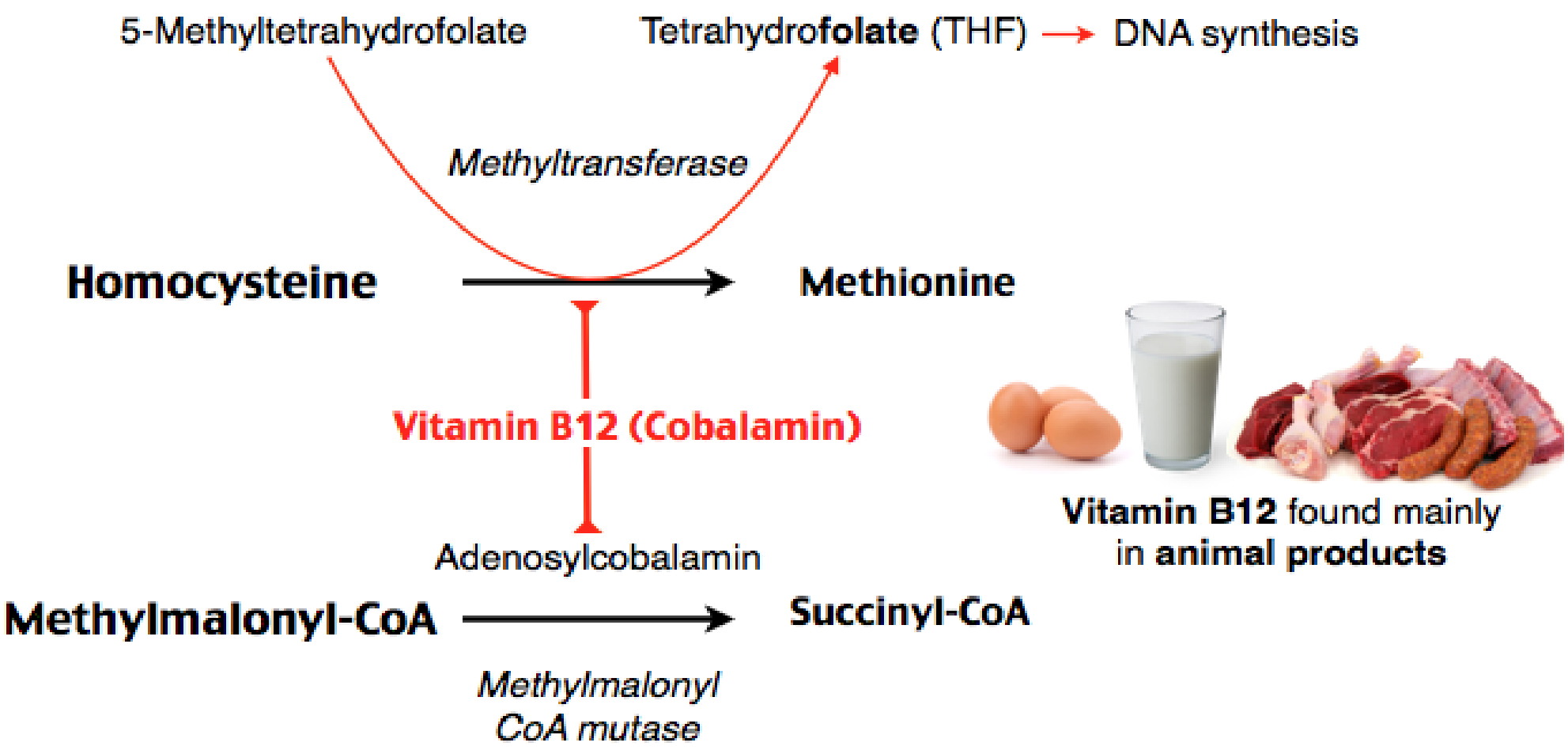
Megaloblastic anaemia

- is a form of anaemia resulted from inhibition of DNA synthesis during RBCs production due to deficiency of vitamin B_{12} or folic acid, or from disturbances in folic acid metabolism
  - MCV >110fL
  - low Hb and RBC count
  - decreased WBC and platelets

- Folate is an important ***substrate of***, and vitamin B_{12} a ***co-factor for***, the generation of the essential amino **acid methionine** from **homocysteine**
- This reaction produces tetrahydrofolate, which is converted to thymidine monophosphate for incorporation into DNA
- Deficiency of either vitamin B_{12} or folate will therefore produce high plasma levels of homocysteine and impaired DNA synthesis, end result is cells with arrested nuclear maturation but normal cytoplasmic development: so-called **nucleocytoplasmic asynchrony**

Vitamin B12 (Cobalamin) Deficiency



- All proliferating cells will exhibit megaloblastosis; so changes are evident in the buccal mucosa, tongue, small intestine, cervix, vagina and uterus
- The high proliferation rate of BM results megaloblastic anaemia

- Cells become arrested in development and die within the marrow; this ***ineffective erythropoiesis*** causing hypercellular marrow

- The haemolysis within the BM results in a raised bilirubin and LDH, but without the **reticulocytosis** , Iron stores are usually raised

- The mature RBC are large and oval, and may contain nuclear remnants immature precursors appear as ‘**giant’ metamyelocytes** with a large ‘sausage-shaped’ nucleus

- The mature neutrophils show hypersegmentation of their nuclei, with six or more nuclear lobes

- In severe cases, a pancytopenia may be present in the peripheral blood

- Vitamin B12 deficiency (but not folate deficiency) is associated with neurological disease in up to **40%** of cases in developing countries

- The main pathological finding is ***focal demyelination of the spinal cord, peripheral nerves, optic nerves and cerebrum***

- The most common manifestations are
  - Sensory-neuropathy
  - peripheral paraesthesia
  - ataxia of gait

Clinical features of megaloblastic anaemia

Symptoms	
• Malaise (90%) • Breathlessness (50%) • Paraesthesia (80%) • Sore mouth (20%) • Weight loss • Impotence	• Poor memory • Depression • Personality change • Hallucinations • Visual disturbance
Signs	
• Smooth tongue • Angular cheilosis • Vitiligo	• Skin pigmentation • Heart failure • Pyrexia

Vitamin B12

Vitamin B12 absorption

- The average daily diet contains (**5–30)µg** of vit B12, mainly in meat, fish, eggs and milk
- The daily requirement (**1µg)**
- In the stomach, gastric enzymes release vitamin B12 from food and at gastric pH , it binds to a carrier protein termed R protein.
- The gastric parietal cells produce intrinsic factor, a vitamin B12-binding protein that optimally binds vitamin B12 at pH **8**
- As gastric emptying occurs, pancreatic secretion raises the pH and vitamin B12 released from the R protein to intrinsic factor
- Bile also contains vitamin B12 that is available for reabsorption in the intestine

- The ***B12–intrinsic factor complex*** binds to specific receptors in the terminal ileum where B12 is actively to the plasma, and binds to transcobalamin II, a transport protein produced by the liver, which carries it to the tissues for utilisation
- The liver stores enough B12 for **3 years** and this, together with the enterohepatic circulation, means that vitamin B12 deficiency takes years to become manifest, even if all dietary intake is stopped or severe B12 malabsorption supervenes

- Blood level of vit B12 (cobalamin) is usually diagnostic of deficiency and remain the first-line test
- Levels of cobalamins fall in normal pregnancy
- Reference ranges vary between laboratories but levels below 150 ng/L are common and, in the last trimester, 5–10% of women have levels below 100 ng/L

Spuriously low B12 values occur in:

- women using the oral contraceptive pill
- patients with myeloma in whom paraproteins can interfere with vitamin B12 assays

Causes of vitamin B12 deficiency

1. **Dietary deficiency**: occurs only in strict vegans

2. **Gastric pathology**

   Hypochlorhydria in elderly patients

   Total gastrectomy invariably results in vitamin B12 deficiency within 5 years, often combined with iron deficiency; these patients need life-long 3-monthly vitamin B12 injections.

   Partial gastrectomy, vitamin B12 deficiency only develops in 10–20% of patients by 5 years; an annual injection of vitamin B12 should prevent deficiency in this group.

3. Pernicious anaemia

- Autoimmune disorder in which the gastric mucosa is atrophic, with loss of parietal cells causing intrinsic factor deficiency
- In the absence of intrinsic factor, **<1%** of dietary vitamin B12 is absorbed
- An average age of onset of 60 years
- It is more common in individuals with other autoimmune disease as (Hashimoto's thyroiditis, Graves' disease, vitiligo or Addison's disease; or a family history of these or pernicious anaemia

❖ ***Investigation for Pernicious***

a. Anti-intrinsic factor Abs in the context of B12 deficiency is **diagnostic** of pernicious anaemia without further investigation

b. Anti-parietal cell antibodies are present in **>90%** of cases but are also present in 20% of normal females over the age of 60 years; a negative result makes pernicious anaemia less likely but a positive result is not diagnostic

c. The Schilling test, involving measurement of absorption of radio-labelled B12 after oral administration before and after replacement of intrinsic factor, has fallen out of favour with the availability of autoantibody tests, greater caution in the use of radioactive tracers, and limited availability of intrinsic factor

4. Small bowel pathology

- 1/3 of patients with pancreatic exocrine insufficiency fail to transfer dietary vitamin B12 from R protein to intrinsic factor usually results in slightly low vitamin B12 values but no tissue evidence of vitamin B12 deficiency

- Motility disorders or hypogammaglobulinaemia can result in bacterial overgrowth can cause vit B12 deficiency. This is corrected to some extent by appropriate antibiotics

- heavy infection with the fish tapeworm develop vitamin B12 deficiency

- Inflammatory disease of the terminal ileum, such as Crohn’s disease, may impair the absorption of vitamin B12–intrinsic factor complex, as may surgery on that part of the bowel

Folate absorption

- Folates are produced by plants and bacteria
  - Rich source: vegetables (spinach, broccoli, lettuce)
  - fruits (bananas, melons)
  - animal protein (liver, kidney)
- An average western diet contains more than the minimum daily intake of 50 μg but excess cooking destroys folates
- Most dietary folate is present as polyglutamates; these are converted to monoglutamate in the upper small bowel and actively transported into plasma where folate is loosely bound to albumin and goes to enterohepatic circulation
- Total body stores of folate are small and deficiency can occur in a matter of weeks

Causes of folate deficiency

1. Poor intake of vegetables especially the edentulous elderly or psychiatric patient
2. Malabsorption e.g. Coeliac disease, small bowel surgery
3. Increased demand
    - Cell proliferation, e.g. haemolysis
    - Pregnancy: twin pregnancies, multiparity and hyperemesis gravidarum
4. Drugs
    - Certain anticonvulsants (e.g. phenytoin)
    - Contraceptive pill
    - Certain cytotoxic drugs (e.g. methotrexate)

- Serum folate measurement is very sensitive to dietary intake

- a single folate-rich meal can normalise it in a patient with true folate deficiency, whereas anorexia, alcohol and anticonvulsant therapy can reduce it in the absence of megaloblastosis

- For this reason, red cell folate levels are a more accurate indicator of folate stores and tissue folate deficiency

Management of megaloblastic anaemia

- If a patient with a severe megaloblastic anaemia is very ill and treatment must be started before vitamin B12 and red cell folate results are available, that treatment should always include both folic acid and vitamin B12

- The use of folic acid alone in the presence of vitamin B12 deficiency may result in worsening of neurological features

- Rarely, if severe angina or heart failure is present , transfusion can be used in megaloblastic anaemia

- The cardiovascular system is adapted to the chronic anaemia present in megaloblastosis, and the volume load imposed by transfusion may result in decompensation and severe cardiac failure. In such circumstances, exchange transfusion or slow administration of 1 U of red cells with diuretic cover may be given

Treatment of Vit B12 deficiency

- In cases of uncomplicated deficiency, is treated with hydroxycobalamin 1000 μg IM for 6 doses 2 or 3 days apart, followed by maintenance therapy of 1000 μg every 3 months for life, is recommended

- In the presence of neurological involvement, a dose of 1000 μg on alternate days until there is no further improvement, followed by maintenance as above, is recommended

- The reticulocyte count will peak by the 5th–10th day after starting replacement therapy. Hb will rise by 10 g/L every week until normalised The BM response is associated with a fall in plasma potassium levels and rapid depletion of iron stores.

- **Treatment of Vit B12 deficiency (continue)**

- If an initial response is not maintained and the blood film is dimorphic (i.e. shows a mixture of microcytic and macrocytic cells), the patient may need additional iron therapy

- A sensory neuropathy may take 6–12 months to correct; long-standing neurological damage may not improve

Treatment of Folate deficiency

- Oral folic acid (5 mg daily for 3 weeks) will treat acute deficiency and 5 mg once weekly is adequate maintenance therapy
- Prophylactic folic acid in pregnancy prevents megaloblastosis in women at risk, and reduces the risk of fetal neural tube defects
- Prophylactic supplementation is also given in chronic haematological disease associated with reduced red cell lifespan (e.g. haemolytic anaemias).
- There is some evidence that supraphysiological supplementation (400 μg/day) can reduce the risk of coronary and cerebrovascular disease by lowering plasma homocysteine levels. This has led the US Food and Drug Administration to introduce fortification of bread, flour and rice with folic acid

Thank you