بسم الله الرحمن الرحيم

Megaloblastic Anemia

Lecture by:

Dr. Zaidan Jayed Zaidan

Learning objectives

At the end of this lecture students should be able to:

1- Define megaloblastic anemia.

2- Identify the metabolism of vitamin B12.

3- Identify the causes of vitamin B12 deficiency.

4- Identify the metabolism of folic acid.

5- Identify the causes of folic acid deficiency.

6- Identify the clinical features of megaloblastic anemia.

7- Identify the investigations of megaloblastic anemia.

8- Recognize the treatment of megaloblastic anemia.

Megaloblastic anaemia

This results from a deficiency of vitamin B12 or folic acid, or from disturbances in folic acid metabolism. Folate is an important substrate of, and vitamin B12a cofactor for, the generation of the essential amino acid methionine from homocysteine. This reaction produces tetrahydro folate, which is converted to thymidine monophosphate for incorporation into DNA. Deficiency of either vitamin B12 or folate will therefore produce high plasma levels of homocysteine and impaired DNA synthesis.

- The end result is cells with arrested nuclear maturation but normal cytoplasmic development: socalled
- nucleocytoplasmic asynchrony. All proliferating cells will exhibit megaloblastosis; hence changes are evident in the buccal mucosa, tongue, small intestine, cervix, vagina and uterus. The high proliferation rate of bone marrow results in striking changes in the haematopoietic system in megaloblastic anaemia. Cells become arrested in development and die within the marrow; this ineffective erythropoiesis results in an expanded hypercellular marrow.

- The megaloblastic changes are most evident in the early nucleated red cell precursors, and haemolysis within the marrow results in a raised bilirubin and lactate dehydrogenase (LDH), but without the reticulocytosis characteristic of other forms of haemolysis . Iron stores are usually raised. The mature red cells are large and oval, and sometimes contain nuclear remnants. Nuclear changes are seen in the immature granulocyte precursors and a characteristic appearance is that of ‘giant’ metamyelocytes with a large ‘sausageshaped’ nucleus. The mature neutrophils show hypersegmentation of their nuclei, with cells having six or more nuclear lobes. If severe, 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, although advanced neurological disease due to B12 deficiency is now uncommon in the developed world.
- The main pathological finding is focal demyelination affecting the spinal cord, peripheral nerves, optic nerves and cerebrum. The most common manifestations are sensory, with peripheral paraesthesiae and ataxia of gait.

24.34 Clinical features of megaloblastic anaemia

Symptoms

- Malaise (90%)
- Breathlessness (50%)
- Paraesthesiae (80%)
- Sore mouth (20%)
- Weight loss
- Altered skin pigmentation
- Impotence
- Poor memory
- Depression
- Personality change
- Hallucinations
- Visual disturbance

Signs

- Smooth tongue
- Angular cheilosis
- Vitiligo
- Skin pigmentation
- Heart failure
- Pyrexia

24.35 Investigations in megaloblastic anaemia

Investigation	Result
Haemoglobin	Often reduced, may be very low
MCV	Usually raised, commonly > 120 fL
Erythrocyte count	Low for degree of anaemia
Blood film	Oval macrocytosis, poikilocytosis, red cell fragmentation, neutrophil hypersegmentation
Reticulocyte count	Low for degree of anaemia
Leucocyte count	Low or normal
Platelet count	Low or normal
Bone marrow	Increased cellularity, megaloblastic changes in erythroid series, giant metamyelocytes, dysplastic megakaryocytes, increased iron in stores, pathological non-ring sideroblasts
Serum ferritin	Elevated
Plasma lactate dehydrogenase (LDH)	Elevated, often markedly

24.36 Neurological findings in B_{12} deficiency

Peripheral nerves

- Glove and stocking paraesthesiae
- Loss of ankle reflexes

Spinal cord

- Subacute combined degeneration of the cord
  - Posterior columns – diminished vibration sensation and proprioception
  - Corticospinal tracts – upper motor neuron signs

Cerebrum

- Dementia
- Optic atrophy

Autonomic neuropathy

Vitamin B12 absorption

- The average daily diet contains 5–30 µg of vitamin B12 ,mainly in meat, fish, eggs and milk – well in excess of the 1 µg daily requirement. 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 B12binding protein which optimally binds vitamin B12 at pH 8. As gastric emptying occurs, pancreatic secretion raises the pH and vitamin B12released from the diet switches from the R protein to intrinsic factor. Bile also contains vitamin B12 which is available for reabsorption in the intestine.

- The vitamin B12–intrinsic factor complex binds to specific receptors in the terminal ileum, and vitamin B12 is actively transported by the enterocytes to plasma, where it binds to transcobalamin II, a transport protein produced by the liver, which carries it to the tissues for utilisation. The liver stores enough vitamin 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 levels of vitamin B12 provide a reasonable indication of tissue stores and are usually diagnostic of deficiency. 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 and in patients with myeloma, in whom paraproteins can interfere with vitamin B12 assays.

Causes of vitamin B12deficiency

Dietary deficiency:

This only occurs in strict vegans but the onset of clinical features can occur at any age between 10 and 80 years. Less strict vegetarians often have slightly low vitamin B12 levels but are not tissue vitamin B12 deficient.

Gastric pathology:

Release of vitamin B12 from the food requires normal gastric acid and enzyme secretion, and this is impaired

by hypochlorhydria in elderly patients or following gastric surgery. Total gastrectomy invariably results in vitamin B12 deficiency within 5 years, often combined with iron deficiency; these patients need lifelong 3-monthly vitamin B12injections. After partial gastrectomy, vitamin B12deficiency only develops in 10–20% of patients by 5 years; an annual injection of vitamin B12 should prevent deficiency in this group.

Pernicious anaemia

- This is an organspecific autoimmune disorder in which the gastric mucosa is atrophic, with loss of parietal cells causing intrinsic factor deficiency. In the absence of intrinsic factor, less than 1% of dietary vitamin B12 is absorbed. Pernicious anaemia has an incidence of 25/100 000 population over the age of 40 years in developed countries, but an average age of onset of 60 years. It is more common in individuals with other autoimmune disease (Hashimoto's thyroiditis, Graves' disease, vitiligo, hypoparathyroidism or Addison's disease) or a family history of these or pernicious anaemia.

- The finding of antiintrinsic factor antibodies in the context of B12 deficiency is diagnostic of pernicious anaemia without further investigation. Antiparietal cell antibodies are present in over 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. The Schilling test, involving measurement of absorption of radiolabelled 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.

Small bowel pathology

- Onethird of patients with pancreatic exocrine insufficiency fail to transfer dietary vitamin B12from R protein to intrinsic factor. This usually results in slightly low vitamin B12values but no tissue evidence of vitamin B12 deficiency.Motility disorders or hypogammaglobulinaemia can result in bacterial overgrowth, and the ensuing competition for free vitamin B12can lead to deficiency. This is corrected to some extent by appropriate antibiotics.A small number of people heavily infected with the fish tapeworm develop vitaminB12 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; hence dietary leafy vegetables (spinach, broccoli, lettuce), fruits (bananas, melons) and animal protein (liver, kidney) are a rich source. 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. Plasma folate is loosely bound to plasma proteins such as albumin and there is an entero hepatic circulation. Total body stores of folate are small and deficiency can occur in a matter of weeks.

Folate deficiency

24.37 Causes of folate deficiency

Diet

- Poor intake of vegetables

Malabsorption

- e.g. Coeliac disease

Increased demand

- Cell proliferation, e.g. haemolysis
- Pregnancy

Drugs*

- Certain anticonvulsants (e.g. phenytoin)
- Contraceptive pill
- Certain cytotoxic drugs (e.g. methotrexate)

*Usually only a problem in patients deficient in folate from another cause.

24.38 Investigation of folic acid deficiency

Diagnostic findings

- Serum folate levels may be low but are difficult to interpret
- Low red cell folate levels indicate prolonged folate deficiency and are probably the most relevant measure

Corroborative findings

- Macrocytic dysplastic blood picture
- Megaloblastic marrow

- The edentulous elderly or psychiatric patient is particularly susceptible to dietary deficiency and this is exacerbated in the presence of gut disease or malignancy. Pregnancyinduced folate deficiency is the most common cause of megaloblastosis worldwide and is more likely in the context of twin pregnancies, multiparity and hyperemesis gravidarum. Serum folate is very sensitive to dietary intake; a single folaterich 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 B12deficiency may result in worsening of neurological deficits.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 cautiously.

Vitamin B12 deficiency

- Vitamin B12deficiency 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. The reticulocyte count will peak by the 5th–10th day after starting replacement therapy. The haemoglobin will rise by 10 g/L every week until normalised. The response of the marrow is associated with a fall in plasma potassium levels and rapid depletion of iron stores. 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; longstanding neurological damage may not improve.

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.

References

1- Davidson's Principle and Practice of Medicine.

2- Harrison's Principles of Internal Medicine.

THANK YOU FOR LISTENING