Patient

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Haemolytic anaemia

What is haemolytic anaemia?

Haemolysis leads to haemolytic anaemia when bone marrow activity cannot compensate for the increased loss of red blood cells (RBCs).

Pathogenesis

Normal red cells have a lifespan of about 120 days. The lifespan may be very short in haemolytic anaemia (eg, as short as five days in sickle cell anaemia).

Haemolysis may occur by two mechanisms:

- Intravascular: due to complement fixation, trauma, or other extrinsic factors. Examples are prosthetic cardiac valves, glucose-6-phosphate dehydrogenase (G6PD) deficiency, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation and paroxysmal nocturnal haemoglobinuria.
- Extravascular (most common): red cells are removed from the circulation by the mononuclear-phagocytic system either because they are intrinsically defective or because of the presence of bound immunoglobulins to their surfaces.

Haemolytic anaemia causes (aetiology)

Genetic

- Red cell membrane abnormalities: hereditary spherocytosis, elliptocytosis.
- Haemoglobin abnormalities: sickle cell anaemia, thalassaemia.
- Enzyme defects: G6PD deficiency, pyruvate kinase deficiency.

Acquired

- Immune:
    - Isoimmune: haemolytic disease of newborn, blood transfusion reaction.
    - Autoimmune haemolytic anaemia:
        - Warm antibody type: idiopathic, systemic lupus erythematosus (SLE), lymphoma, chronic lymphocytic leukaemia (CLL), Evans' syndrome (thrombocytopenia associated with a positive direct Coombs' test).
        - Cold antibody type: cold haemagglutinin disease, paroxysmal cold haemoglobinuria, *Mycoplasma pneumoniae*, lymphoma, infectious mononucleosis or other viral infections
        - Drug-related: drug absorbed on to red cell surface (eg, penicillins, cephalosporins) or immune complex mediated (eg, sulfonamides, sulfasalazine) [1] .
- Non-immune: trauma (cardiac haemolysis, microangiopathic anaemia (found in patients with disseminated intravascular coagulation or haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura), infection (malaria, sepsis), hypersplenism, membrane disorders, paroxysmal nocturnal haemoglobinuria, liver disease.

Epidemiology

- Risk factors are variable and depend on the underlying cause.
- Sickle cell disorders mainly affect Africans and some Arabian peoples [2] .
- G6PD deficiency has several variants, divided into five classes according to the level of enzyme activity. These have typical geographical spread. Common locations are the Middle East and the Mediterranean [3] .

- Autoimmune haemolytic anaemia is slightly more common in females than in males. Most often, it presents in middle-aged and older individuals.

Presentation

Haemolytic anaemia symptoms

- Haemolytic anaemia symptoms are due to both anaemia and the underlying disorder. Patients with minimal or long-standing haemolytic anaemia can be asymptomatic.
- Severe haemolytic anaemia, especially of sudden onset, may cause tachycardia, dyspnoea, angina and weakness.
- Gallstones may cause abdominal pain. Bilirubin stones can develop in patients with persistent haemolysis.
- Haemoglobinuria can occur in patients with intravascular haemolysis and it produces dark urine.
- Medication history:
    - Some medications (eg, penicillin, quinine and L-dopa) may cause immune haemolysis.
    - Oxidant drugs (eg, nalidixic acid) - and also fava beans and infections - can trigger haemolysis in patients with G6PD deficiency.

Signs

- Signs of haemolytic anaemia: general pallor and pale conjunctivae. Tachycardia, tachypnoea and hypotension if severe.
- Mild jaundice may occur due to haemolysis.
- Splenomegaly: occurs with some causes - eg, hereditary spherocytosis. It may indicate an underlying condition such as CLL, lymphoma or SLE.
- Leg ulcers may occur in some causes of haemolytic anaemia - eg, sickle cell anaemia.

- Right upper abdominal quadrant tenderness may indicate gallbladder disease.
- Bleeding and petechiae indicate thrombocytopenia due to Evans' syndrome or thrombotic thrombocytopenic purpura if neurological signs are also present.
- Signs of underlying disorder - eg, malar rash in patients with SLE.

Investigations[4]

Nonspecific findings

- FBC:
    - Platelet count: normal in most haemolytic anaemias. Thrombocytopenia can occur in SLE, CLL and microangiopathic haemolytic anaemia (defective prosthetic cardiac valves, thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome and disseminated intravascular coagulation).
    - A normal MCV and mean corpuscular haemoglobin (MCH): consistent with a normocytic hypochromic anaemia[5] .
    - High MCH and MCH concentration (MCHC): suggest spherocytosis.
- When red cells rupture, they release lactose dehydrogenase (LDH). Raised levels of LDH are therefore often seen. Bilirubin levels may also be raised due to the same mechanism.
- The level of haptoglobin may be reduced as this binds to free haemoglobin.
- Coombs' test: the direct Coombs' test is used clinically when immune-mediated haemolytic anaemia (antibody-mediated destruction of RBCs) is suspected.
- Cold agglutinins: a high titre of anti-I antibody may be found in mycoplasma infections and a high titre of anti-I antibody may be found in haemolysis associated with infectious mononucleosis. An anti-P cold agglutinin may be seen in paroxysmal cold haemoglobinuria.

- Ultrasound to estimate spleen size: physical examination is not reliable.
- CXR and ECG: may be needed to assess cardiopulmonary status.

Assess presence of haemolysis

- Red cell destruction:
    - Reduced haemoglobin.
    - Spherocytes, fragmented red cells, nucleated red cells or other abnormal red cells.
    - Increased serum unconjugated bilirubin, increased lactate dehydrogenase (LDH) and reduced or absent haptoglobin.
    - Increased urinary urobilinogen, haemosiderinuria.
- Increased red cell production:
    - Increased reticulocytosis: may also be due to blood loss or a bone marrow response to iron, vitamin B12 or folate deficiencies.
    - Increased red cell MCV (due to reticulocytosis; however, there are many other causes - eg, vitamin B12 and folate deficiency.

Determine if the haemolysis is intravascular

- Increased plasma haemoglobin.
- Methaemoglobinaemia.
- Haemoglobinuria.

Identify the cause of haemolytic anaemia

- Genetic:
    - Red cell morphology: spherocytes (suggest congenital spherocytosis or autoimmune haemolytic anaemia), elliptocytes, schistocytes (fragmented red cells suggesting thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome or mechanical damage).
    - Screen for sickle cell: sickling under reduced conditions.
    - Haemoglobin electrophoresis.
    - Red cell enzyme assays.
- Acquired:
    - Antibodies: IgG warm antibodies in autoimmune haemolytic anaemia react at 37°C whereas IgM cold antibodies react at lower temperatures, ie 20°C or below[6] . The direct antiglobulin test is usually, although not always, positive in autoimmune haemolytic anaemia.
    - Red cell morphology: eg, haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura.

Haemolytic anaemia treatment and management[4]

General measures

Administer folic acid because active haemolysis may cause folate deficiency.

Discontinue medications that may have precipitated or aggravated haemolysis.

Further specific treatment depends upon the cause.

Transfusion therapy

Whilst transfusions are the mainstay of treatment for severe anaemia, they should otherwise be avoided, due to adverse effects.

Use the least incompatible blood if transfusions are indicated. The risk of acute haemolysis of transfused blood is high but the degree depends on the rate of infusion.

Other emergency treatment

Plasmapheresis or diuresis may be required in severe cases, depending on the underlying cause.

Iron therapy

This is indicated for patients with severe intravascular haemolysis in which persistent haemoglobinuria has caused substantial iron loss.

NB: iron stores increase in haemolysis and so iron administration is generally contra-indicated in haemolytic disorders, particularly those that require chronic transfusion support.

Autoimmune haemolytic anaemia therapy

Corticosteroids are indicated for the warm type. Other immunosuppressive drugs (eg, azathioprine and cyclophosphamide) may be required if steroids fail[7] . Rituximab - a monoclonal antibody against CD20 - has been successfully used in refractory idiopathic autoimmune haemolytic anaemia in children. Other options which have been tried include danazol, cyclophosphamide or alemtuzumab[6] .

The haemolytic anaemia in cold type is usually mild and there is no need for correction. Management includes keeping extremities warm. Steroids and splenectomy are less successful and transfusions should be avoided if possible.

Splenectomy

This may be the first choice of treatment in some types of haemolytic anaemia such as hereditary spherocytosis[8] . In other cases it is recommended when other measures have failed.

Splenectomy is usually not recommended in haemolytic disorders such as cold agglutinin haemolytic anaemia.

Complications

- Haemolytic anaemia may lead to high-output cardiac failure.

- Jaundice creates problems associated with increased unconjugated bilirubin.
- In patients with intravascular haemolysis, iron deficiency due to chronic haemoglobinuria can exacerbate anaemia and weakness.

Further reading

- The diagnosis and management of primary autoimmune haemolytic anaemia; British Committee for Standards in Haematology (2016)
- Guidelines on the management of drug-induced immune and secondary autoimmune, haemolytic anaemia; British Committee for Standards in Haematology (2016)

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