*Heamatological diseases*

# *Heamolytic Anemia II*

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# ACQUIRED HAEMOLYTIC ANAEMIA *Causes*

- *Immune*

1. Autoimmune
   - Warm
   - Cold
2. Alloimmune
   - Haemolytic transfusion reactions
   - Haemolytic disease of the newborn
   - After allogeneic bone marrow or organ transplantation
3. Drug-induced

- *Non-immune*

1. Acquired membrane defects
   - Paroxysmal nocturnal haemoglobinuria
2. Mechanical
   - Microangiopathic haemolytic anaemia
   - Valve prosthesis
   - March haemoglobinuria
3. Secondary to systemic disease

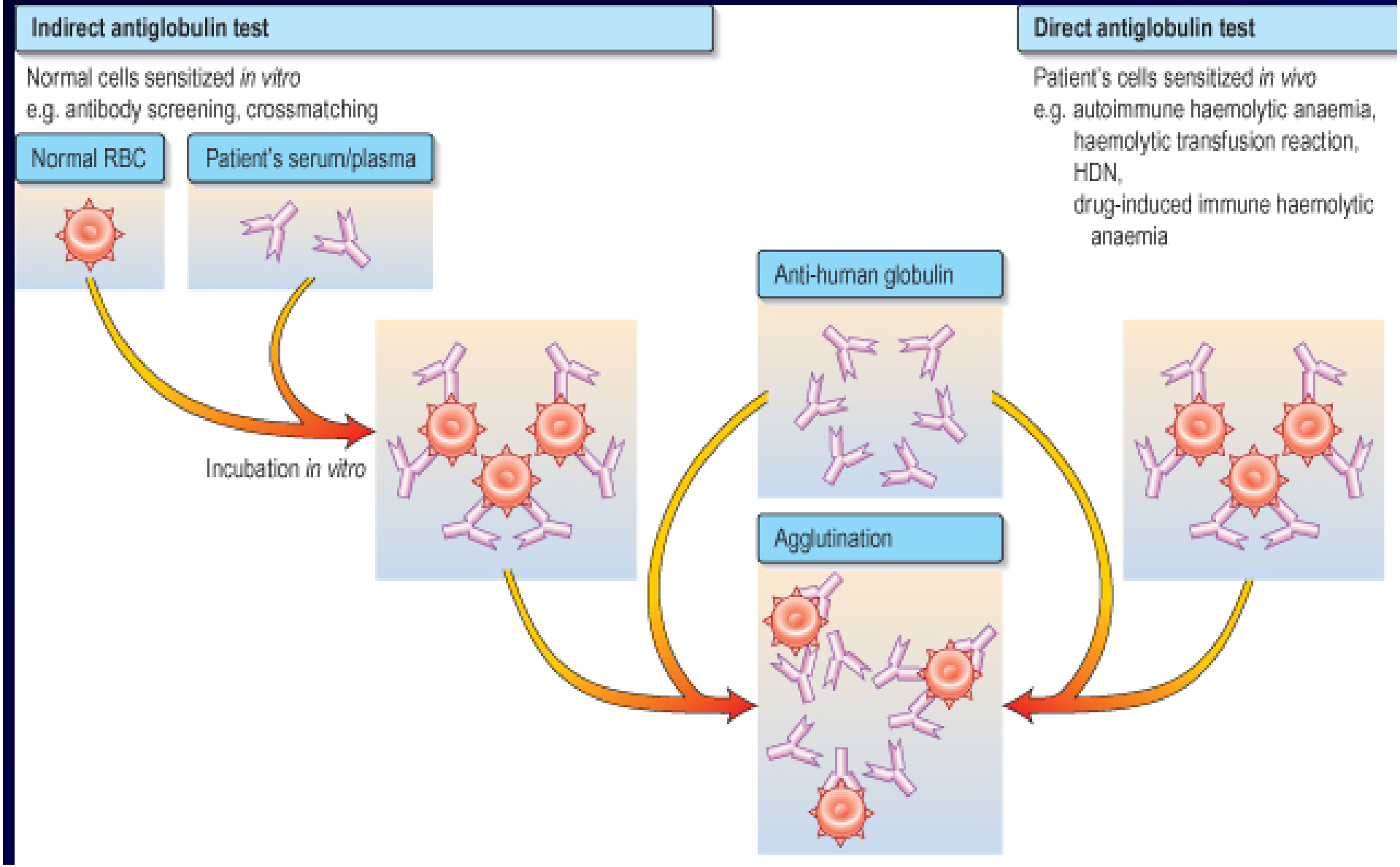
# AUTOIMMUNE HAEMOLYTIC ANAEMIAS (AIHA)

- Autoimmune haemolytic anaemias (AIHA) are acquired disorders resulting from increased red cell destruction due to red cell autoantibodies.
- These anaemias are characterized by the presence of a positive direct antiglobulin (Coombs') test, which detects the autoantibody on the surface of the patient's red cells.
- AIHA is divided into 'warm' and 'cold' types, depending on whether the antibody attaches better to the red cells at body temperature (37°C) or at lower temperatures.

# AIHA
## *Mechanism of RBC destruction*

- IgM or IgG red cell antibodies which fully activate the complement cascade cause lysis of red cells in the circulation (intravascular haemolysis).
- IgG antibodies frequently do not activate complement and the coated red cells undergo extravascular haemolysis

# Antiglobulin (Coomb's) test



# major features of AIHA

| | *warm* | *cold* |
|---|---|---|
| Temp. at which AB attaches best to RBC | 37°C | Lower than 37°C |
| Type of antibody | IgG | IgM |
| Direct Coombs' test | Strongly positive | positive |
| Causes of primary conditions | Idiopathic | Idiopathic |
| Causes of secondary condition | - Autoimmune disorders, e.g. SLE,<br>- Chronic lymphocytic leukaemia,<br>- Lymphomas, Carcinoma<br>-Drugs, methyldopa | - Infections, e.g. infectious mononucleosis, *Mycoplasma* pneumonia<br>- Lymphomas |

# 'Warm' AIHA

- These anaemias may occur at all ages and in both sexes, although they are most frequent in middle-aged females.
- They can present as a short episode of anaemia and jaundice but they often remit and relapse and may progress to an intermittent chronic pattern. The spleen is often palpable.
- Infections or folate deficiency may provoke a profound fall in the haemoglobin level. In more than 30% of cases.
- These anaemias may be associated with lymphoid malignancies or diseases such as rheumatoid arthritis and SLE .

# Investigations

- Haemolytic anaemia is evident.
- Spherocytosis is present as a result of red cell damage.
- Direct antiglobulin test is positive, with either IgG alone (67%), IgG and complement (20%), or complement alone (13%) being found on the surface of the red cells.
- Autoimmune thrombocytopenia and/or neutropenia may also be present (Evans' syndrome).

# Treatment and prognosis

1. **Corticosteroids** (e.g. prednisolone in doses of 1 mg/kg daily) are effective in inducing a remission in about 80% of patients. Steroids reduce both production of the red cell autoantibody and destruction of antibody-coated cells.

2. **Splenectomy** may be necessary if there is no response to steroids or if the remission is not maintained when the dose of prednisolone is reduced.

3. **Other immunosuppressive drugs**, such as azathioprine and cyclophosphamide, may be effective in patients who fail to respond to steroids and splenectomy.

# ‘Cold‘ AIHA

- Normally, low titres of IgM cold agglutinins are present in plasma and are harmless.
- At low temperatures these antibodies can attach to red cells and cause their agglutination in the cold peripheries.
- In addition, activation of complement may cause intravascular haemolysis when the cells return to the higher temperatures in the core of the body.
- After certain infections (such as *Mycoplasma*, CMV, EBV) there is increased synthesis of cold agglutinins producing haemolysis.

## ***Chronic cold haemagglutinin disease (CHAD)***

This usually occurs in the elderly with a gradual onset of haemolytic anaemia owing to the production of monoclonal IgM cold agglutinins. After exposure to cold, the patient develops an acrocyanosis similar to Raynaud's as a result of red cell autoagglutination.

# *Investigations*

1. Red cells Agglutination is sometimes seen in the sample tube after cooling. The agglutination is reversible after warming the sample.
2. Direct antiglobulin test is positive with complement alone.
3. Monoclonal IgM antibodies may be detected.

## ***Treatment***

1. The underlying cause should be treated, if possible. Patients should *avoid exposure to cold*.
2. Treatment with steroids, immunosuppressives and splenectomy is usually ineffective.

# DRUG-INDUCED IMMUNE HAEMOLYTIC ANAEMIA

- *The interaction between a drug and red cell membrane produces a composite antigenic structure, provoking two types of antibodies:*

1. ***Drug-dependent antibodies***
   - Bind to both the drug and the cell membrane but not to either separately.
   - Clinically there is usually severe complement-mediated intravascular haemolysis.
   - Resolves quickly after withdrawal of the drug.

1. ***Drug-independent antibodies***

   - Induced by alteration of the red cell membrane.
   - React with red cells in vitro in the absence of the drug and are indistinguishable from 'true' autoantibodies.
   - There is extravascular haemolysis and the clinical course tends to be more prolonged.

- This concept also applies to drug-induced thrombocytopenia and neutropenia.

# ALLOIMMUNE HAEMOLYTIC ANAEMIA

- *Antibodies produced in one individual react with the red cells of another. This situation occurs in:*

1. Haemolytic disease of the newborn.
2. Haemolytic transfusion reactions.
3. After allogeneic bone marrow, renal, liver or cardiac transplantation when donor lymphocytes ('passenger lymphocytes') may produce antibodies against the recipient red cell and cause haemolytic anaemia.

# Haemolytic disease of the newborn (HDN)

- HDN is due to fetomaternal incompatibility for red cell antigens.
- Maternal antibodies against fetal red cell antigens pass via the placenta into the fetus, where they destroy the fetal red cells.
- Only IgG antibodies are capable of transplacental passage.

# Haemolytic disease of the newborn (HDN)

1. *ABO incompatibility;*

- The most common type of HDN, where the mother is usually group O and the fetus group A. - HDN due to ABO incompatibility is usually mild and exchange transfusion is rarely needed.

## 2. *RhD incompatibility*

- RhD -ve mother and RhD +ve fetus
- Sensitization occurs as a result of passage of fetal red cells into the maternal circulation (which most readily occurs at the time of delivery), so that first pregnancies are rarely affected.

- However, sensitization may occur at other times, for example after abortion, ectopic pregnancy or due to transplacental bleeding.

## *Clinical features* of HDN

1. These vary from a mild haemolytic anaemia of the newborn to intrauterine death from 18 weeks' gestation with the characteristic appearance of hydrops fetalis (hepatosplenomegaly, oedema and cardiac failure).

2. Kernicterus occurs owing to severe jaundice in the neonatal period and bile pigment deposition occurs in the basal ganglia.

-This can result in permanent brain damage, choreoathetosis, convulsions and spasticity.

-In mild cases it may present as deafness.

# ***Investigations***

1. **Routine antenatal serology**;

   - All mothers should have their ABO and RhD groups determined and their serum tested for atypical antibodies.

   - If an antibody is detected, its blood group specificity should be determined and the mother should be retested at least monthly.

   - A rising IgG antibodies titre or a history of HDN in a previous pregnancy is an indication for referral to a specialist unit.

2. **Ultrasound**;

   - Shows changes in the fetal blood flow and cardiac function caused by compensated anaemia

   - Can be demonstrated in utero before hydrops develops.

- ***Investigations***

At the birth of an affected infant, sample of cord blood is obtained. This shows:

1. Anaemia with reticulocytosis
2. Positive direct antiglobulin test
3. Raised serum bilirubin.

# HDN; *Treatment*

- *Management of the baby*

1. In mild cases, phototherapy may be used to convert bilirubin to water-soluble biliverdin.

- Biliverdin can be excreted by the kidneys and this therefore reduces the chance of kernicterus.

- In more severe cases, exchange transfusion may be necessary to replace the infant's red cells and to remove bilirubin.

- ***Prevention of RhD immunization in the mother***

Anti-D should be given after delivery when all of the following are present:

1. the mother is RhD negative
2. the fetus is RhD positive
3. there is no maternal anti-D detectable in the mother's serum; i.e. the mother is not already immunized.

- The dose is 500 i.u. of IgG anti-D intramuscularly within 48 hours of delivery.

# NON-IMMUNE HAEMOLYTIC ANAEMIA

## *A) Paroxysmal nocturnal haemoglobinuria (PNH)*

- This is a rare acquired red cell defect in which a clone of red cells is particularly sensitive to destruction by activated complement.

- These cells are continually haemolysed intravascularly.

- Platelets and granulocytes are also affected and there may be thrombocytopenia and neutropenia.

- The underlying defect is an inability of PNH cells to make glycosylphosphatidylinositol (GPI), which anchors surface proteins and in their absence the haemolytic action of complement continues. The molecular basis of PNH has been found to be mutations in the *pig*-A (phosphatidylinositol glycan protein A) gene responsible for synthesis of the GPI anchor.

# PNH; Clinical features

The major clinical signs are

**1) intravascular haemolysis**:

precipitated by infection or surgery.

**2) venous thrombosis:**

Venous thrombotic episodes are very common and severe thromboses may occur, for example in hepatic, mesenteric or cerebral veins. The cause is not known.

**3) haemoglobinuria:**

Characteristically only the urine voided at night and in the early morning is dark in colour, although the reason for this phenomenon is not clear. In severe cases all urine samples are dark.

**4) Some patients present with signs of anaemia**

Urinary iron loss may be sufficient to cause iron deficiency.

# Treatment

1. Supportive measures such as blood transfusions. Leucocyte-depleted blood should be used in order to prevent transfusion reactions resulting in complement activation and acceleration of haemolysis.

2. Long-term anticoagulation may be necessary for patients with recurrent thrombotic episodes.

# Prognosis

- The course of PNH is variable.
- PNH may transform into aplastic anaemia or acute leukaemia
- PNH may remain stable for many years and the PNH clone may even disappear.

# MECHANICAL HAEMOLYTIC ANAEMIA

- Red cells may be injured by physical trauma in the circulation.
- Direct injury may cause immediate cell lysis or followed by resealing of the cell membrane with the formation of distorted red cells or 'fragments'. These cells may circulate for a short period before being destroyed prematurely in the reticuloendothelial system.

***Causes of mechanical haemolytic anaemia include:***

1. Damaged artificial heart valves

2. March haemoglobinuria, where there is damage to red cells in the feet associated with prolonged marching or running

3. Microangiopathic haemolytic anaemia (MAHA)

where fragmentation of red cells occurs in an abnormal microcirculation caused by

* malignant hypertension
* eclampsia
* haemolytic uraemic syndrome
* thrombotic thrombocytopenic purpura
* vasculitis
* disseminated intravascular coagulation(DIC)