Supplementary notes on thalassaemia

**THALASSAEMIA IS PREVALENT IN HONG KONG**

The thalassaemias are **genetic disorders of globin chain synthesis** characterized by a reduction in the synthesis of particular globin chains. This results in an imbalance in the available quantity of different normal chains. The excess chains present polymerize but they are unstable and precipitate out of solution in RBC. This leads to early destruction of RBC precursors in the bone marrow (ineffective erythropoiesis) or shortening of RBC life span. Defective haemoglobinization results in **hypochromic microcytic** red cells. Moreover, abnormal globin tetramers (Hb Barts or Hb H) or normal haemoglobin present in unphysiological amount (Hb F - $\alpha_2\gamma_2$) have increased oxygen affinity and contribute to tissue hypoxia.

The thalassaemias constitute one of the most common single gene disorders occurring in a broad geographical region stretching from the Mediterranean through the Middle East and India to South East Asia.

**The $\alpha$-thalassaemias**

Alpha-globin chain is required for the production of both fetal ($\alpha_2\gamma_2$) and adult ($\alpha_2\beta_2$) haemoglobin, and $\alpha$-thalassaemia results in defective fetal and adult haemoglobin production. In the fetus, excess $\gamma$ chains form $\gamma_4$ tetramers (Hb-Barts), whereas in adults excess $\beta$ chains form $\beta_4$ (Hb H).

Four principal clinical states occur according to the number of genes deleted:

a) **$\alpha$-thal 2** (single gene deletion)

Individuals carrying this $\alpha$-thalassaemia trait usually have normal haematological findings. It can be detected by DNA analysis.

b) **$\alpha$-thal 1** (2-gene deletion)

Individuals with this $\alpha$-thalassaemia trait have normal to slightly reduced haemoglobin, increased red cell count and hypochromic microcytic red cells. Hb H inclusions can be precipitated out of solution to form blue green granules when RBC are incubated with brilliant cresyl blue stain.

c) **Hb H disease** (3-gene deletion)

Gross imbalance of chain production results in chronic anaemia. Excess $\beta$ chain polymerize to form Hb H, and the level of Hb H ranges from 5% to more than 40% of the total haemoglobin. Small amount of Hb Barts may be present.

The clinical picture of Hb H disease is very **variable**, with the usual features being anaemia, splenomegaly and hepatomegaly. Nearly all patients have normal physical development, although a small proportion has thalassaemic facies. The commonest complication is the
development of hypersplenism, in which case splenectomy is indicated. The patients are generally not transfusion dependent.

d) Hydrops fetalis

In this condition all the 4 genes encoding the α-chain are deleted and no α-chain is found. This condition is incompatible with life. Excess γ-chains produced in fetal period polymerize to form Hb Barts (γ₄). The fetus is edematous due to heart failure (as a result of anaemia) and can be diagnosed on ultrasonography.

**Molecular genetics of α thalassaemia**

Around 90% of α-thalassaemia defects are due to deletions of DNA with the remaining 10% being of the non-deletional type. Deletion in the vast majority of cases of α-thal-1 in Southeast Asia removes 18.0 kb of DNA from the α-gene cluster. The disorder α-thal-2 is caused by the removal of one α-gene by one of two ways: a deletion of 4.2 kb or 3.7 kb of DNA from the α-globin gene cluster. Examples of non-deletional defects include Hb-Constant Spring and Hb-Quong Sze.

**The β-thalassaemias**

The β-thalassaemias are characterized by reduced (β⁺) or absent (β⁰) synthesis of β-globin chain. Since β-chain production becomes predominant only in post-natal period, the severe form of β-thalassaema (Cooley’s anaemia) becomes manifest, only when the patient is 3 months old or later. Clinical types of β-thalassaemia include heterozygous β-thalassaemia (β-thal trait), β-thalassaemia major (Cooley’s anaemia) and thalassaemia intermedia.

A). Heterozygous β-thalassaemia (β-thalassaemia minor/trait)

Typically, individuals heterozygous for β⁰ or β⁺ thalassaemia are asymptomatic with slightly reduced haemoglobin levels, reduced MCV & MCH, and elevated red cell count. The single most important diagnostic feature of an individual with heterozygous β-thalassaemia is a raised level of HbA₂ (4-7%). Many β-thalassaemia heterozygotes have minor elevations of HbF (1-3%).

B). Cooley’s anaemia (β-thalassaemia major)

There is either a total absence or a marked reduction of β-globin chains, leading to excessive α-globin chains which precipitate out in the red cell precursors causing extensive intramedullary destruction of red cell precursors (ineffective erythropoiesis) with consequent marked expansion of the bone marrow. In addition there is some increased destruction of peripheral blood red cells (haemolytic element). Red cells containing increased levels of Hb F survive selectively, and this explains the high level of Hb F.

The blood film shows marked red cell anisocytosis and poikilocytosis. Most red cells are very hypochromic and circulating nucleated reds are numerous. In homozygous β⁰ thalassaemia, there is complete absence of HbA, small amounts of HbA₂ with the remainder (around 98%) being HbF. The equivalent haemoglobin pattern of homozygous β⁺
thalassaemia is more variable, with HbF levels around 60%, although a wide range can be found.

Patients suffering from Cooley’s anaemia have typical thalassaemic facies, protuberant abdomen (hepatosplenomegaly) and poor musculoskeletal development. They are likely to experience complications including recurrent infections, spontaneous fractures, hypersplenism, leg ulcers and extramedullary haemopoiesis. Treatment with blood transfusion lead to iron overload.

C). Thalassaemia intermedia

Thalassaemia intermedia refer to the clinical syndrome in which patients are symptomatic but have a milder clinical disorder than Cooley’s anaemia.

The three major factors that modify disease severity in β-thalassaemia major are:

- nature of the β-globin gene defect (i.e. whether the mutation is associated with a severe phenotype or not).
- genetic determinants of HbF level.
- The configuration of α-globin gene locus (this affects the degree of α and β globin gene imbalance).

Molecular genetics of β-thalassaemia

In contrast to α-thalassaemia, the majority of β-thalassaemias is caused by point mutations rather than by gene deletions. There are over 90 different β globin mutations worldwide; each racial group (Chinese, Mediterraneans, Africans and Asia Indians) have its own unique set of mutations.

Laboratory diagnosis of thalassaemia

- complete blood count, red cell indices.
- peripheral blood smear examination.
- haemoglobin electrophoresis.
- quantitation of HbF by alkaline denaturation.
- quantitation of HbA₂ by chromatography.
- detection of Hb H inclusions.

Prevention of hydrops fetalis and Cooley’s anaemia

- public health education.
- counselling of specific target groups, e.g. couples before and soon after marriage.
- carrier detection.
- prenatal diagnosis.

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