THALASSEMIAS AND HEMOGLOBINOPATHIES

What are Thalassemias and Hemoglobinopathies?

Thalassemias are characterized by a decreased production in either the **α** or ß globin chains. They are grouped into **α** and ß thalassemias.

Hemoglobin variants, on the other hand, are structural abnormalities and are usually due to a single amino acid substitution.

Alpha Thalassemias

Alpha thalassemia may result from a defect in the alpha globin genes. There are 4 alpha globin genes so the defect or loss may be from one to four of the genes. The clinical symptomatology will depend on the number of gene deletions/mutations. The loss of 4 genes results in **hydrops fetalis** which is fatal in utero. Loss of 3 genes indicates Hb H disease which may manifest later in childhood as moderately severe anemia. Iron overload, secondary to either ineffective erythropoiesis or transfusion therapy, becomes a major problem when these patients reach puberty and adulthood. Loss of 2 genes (trait) or 1 (silent carrier) may result in mild anemia and these two are clinically insignificant.

The percentage of hemoglobin Bart's at birth may indicate the number of alpha gene loss. If the percentage is < 10% then the infant may have 1 or 2 gene loss. If the amount of Bart's is >20-25% then it may indicate a more severe form of alpha thalassemia such as Hb H disease. Non-deletional forms of Hb H disease such as Hb H Constant Spring are clinically more severe.

Clinical Signs of Alpha Thalassemia

Loss of 1 or 2 **α** genes is asymptomatic with mild anemia at most. The smear will show microcytosis which is often mistaken for iron deficiency anemia. A child who does not respond to iron therapy for his/her anemia should be worked up for possible thalassemia. Iron supplements should be avoided thereafter. Parents of this child should be assured that he or she will be symptom-free but they should also be made aware that the trait may run in their family. Folic acid is recommended for patients with alpha thalassemia with anemia.

Hb H disease is due to deletion of 3-alpha genes resulting in the formation of beta tetramers (ß4). Clinically, this is classified as a form of **thalassemia intermedia**. A non-deletional form of HbH disease such as **Hb H Constant Spring** is seen when 2 alpha gene deletion such as the --SEA deletion is seen in conjunction with an **α** gene mutation such as the Constant Spring mutation. Patients may have a variable clinical course with some pallor and jaundice after febrile episodes which may require transfusions or severe anemia requiring regular transfusions early in childhood resulting in iron overload later on in life. This may result in growth stunting, delayed sexual maturity, and heart failure if uncorrected. These patients would require early referral to a hematologist.

Important Considerations:

- Coordination with a pediatric hematologist is advised to evaluate iron status of the patient before giving empiric iron supplements.
- Immunizations are not contraindicated for this condition and may be given as recommended by the Philippine Pediatric Society.

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Beta Thalassemias

Beta Thalassemia mutations may result in total absence of beta chain production (ß°) or partial reduction of the chain (ß+). A presumptive diagnosis of ß thalassemia in the newborn is made if the Hb F is the sole hemoglobin with absent or markedly decreased Hb A. Decreased hemoglobin production leads to microcytosis, ineffective erythropoiesis and skeletal changes. A carrier state of beta thalassemia may be missed at birth because of the absence of Hgb A2 early in the neonatal period.

Clinical features may vary depending on the complete or partial absence of the beta chain. Beta thalassemia major patients (ß°ß°) seem healthy after birth but develop symptoms within the first year of life. They are transfusion dependent as early as the late infancy period while thalassemia intermedia (ß°ß+) or (ß+ß+) has less severe anemia and require less frequent transfusions. Patients presenting with thalassemia intermedia phenotype during childhood often become transfusion dependent as adults due to worsening anemia and fatigue. They may eventually develop iron overload and may succumb to cardiac failure later in life.

Children heterozygous for a normal and a beta thalassemia gene will have very mild anemia, microcytosis, and slight splenomegaly. Blood transfusion is usually not required.

There are individuals who are compound heterozygote for Hb E and ß° thalassemia. Hb E/ß^a thalassemia presents in infancy as variably severe anemia with clinical phenotype ranging from complete lack of symptoms to transfusion dependence. Osteoporosis, iron overload, growth failure, pulmonary hypertension are commonly reported in both transfused and non-transfused patients.

Patients with beta thalassemia major are best managed in a specialized hospital as they will need regular transfusions and iron chelation. Those with the minor form of the disease will not need special care. However, it is important to have their future partner screened for the trait as their union may result in a baby with a severe case of thalassemia. Intermedia parents may need specialized care later in childhood as iron overload may present later in life so inadvertent and prolonged use of iron are discouraged in these patients.

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Hemoglobin E

Hemoglobin E (Hb E) is a variant hemoglobin with a mutation in the ß-globin gene causing substitution of glutamic acid for lysine at position 26 of the ß globin chain. Hb E is the most common hemoglobinopathy variant in South East Asia. The ßE chain is synthesized at a reduced rate leading to an imbalance in the globin chains. **Hb E** disease is defined by the coexistence of two ßE alleles, resulting in a homozygous state EE.

Individuals with the genotype EE are usually completely asymptomatic. Hemoglobin level may be low and red cell indices are likewise low with significant morphological abnormalities including increased numbers of target cells. Homozygous Hb E individuals do not warrant special care.

Hb E trait is defined by the heterozygous condition associating with one normal adult hemoglobin (Hb A) ß gene and one variant hemoglobin E ß gene. Hb E trait does not exhibit clinical disease. There may be slight anemia with microcytosis. Target cells are also seen in the smears. In most cases, children are symptom-free and will have normal growth and development.

In regions where there is a high incidence of **α** and ß thalassemias such as the Philippines, Hb E may be co-inherited with these disorders. Interactions with various forms of **α** and ß thalassemia produce a very wide range of clinical syndromes of varying severity. Hb E with **Hb H** may result in moderately severe thalassemic findings similar to thalassemia intermedia. **Hb E/ß°** on the other hand, may behave as thalassemia major and will need to be managed in a specialty center.

Important Considerations:

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- Immunizations are not contraindicated for this condition and may be given as recommended by the Philippine Pediatric Society.

Other Hemoglobinopathies

Sickle Cell

Sickle cell disease patients have predominant Hb S. This condition is most common in Africa, Middle East and the United States. Affected infants are usually normal at birth but develop anemia later when the Hb S concentration increases and the Hb F decreases. These patients are particularly susceptible to encapsulated bacterial infections such as Streptococcus pneumonia, Hemophilus influenzae, Staphylococcus aureus, and Salmonella. Prophylactic penicillin should be started early in infancy once diagnosis is made.

Heterozygotes (Hb AS) are usually asymptomatic and are referred to as sickle cell trait. In most cases, these children are symptom free and will have normal growth and development.

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Hemoglobin C

Hemoglobin C (Hb C) is a variant hemoglobin with a mutation in the ß globin gene causing substitution of glutamic acid for lysine at position 6 of the globin chain. Hb C disease is defined by the co-existence of 2 ßC alleles (homozygous state CC). Individuals with Hb C disease may have compensated hemolysis or mild to moderate anemia. They may also have splenomegaly and increased risk of cholelithiasis due to chronic hemolysis. This disorder is most common in individuals of African descent.

Hb C trait on the other hand is defined by the heterozygous condition associated with one normal adult hemoglobin (Hb A) gene and one variant HbC ß gene. Individuals with Hb C trait are clinically asymptomatic. Hemoglobin level is usually normal but mild microcytosis is common. This hemoglobin variant may be co-inherited with alpha thalassemia and beta thalassemia which may result in more serious clinical manifestations.

Hemoglobin D

Hemoglobin D (Hb D) is a variant hemoglobin with a mutation in the ß globin gene causing substitution of glutamine for glutamic acid in the ß globin chain. Hb D disease is defined by homozygous state DD. Individuals with Hb D disease are usually clinically asymptomatic. However, mild haemolytic anemia may develop in the first few months of life.

Hb D trait is defined by the heterozygous condition associated with one normal adult hemoglobin and one variant Hb D ß gene. Individuals with Hb D trait are clinically asymptomatic. This hemoglobin variant may also be co-inherited with alpha thalassemia and beta thalassemia which may result in more serious clinical manifestations.

Important Considerations:

- Coordination with a pediatric hematologist is advised to evaluate iron status of the patient before giving empiric iron supplements.
- Immunizations are not contraindicated for this condition and may be given as recommended by the Philippine Pediatric Society.

References:
Bachir D and F Galecteros. Hemoglobin C disease. Orphanet. November 2004. Retrieved from: https://www.orpha.net/data/patho/GB/uk-HbC.pdf
Bachir D and F Galecteros. Hemoglobin E disease. Orphanet. November 2004. Retrieved from: https://www.orpha.net/data/patho/GB/uk-HbE.pdf
Hoppe, C., Newborn Screening for Non- Sickling Hemoglobinopathy, ASH Education Book, 2009.
Hoyer, J. 79 Hemoglobinopathies.Annual Meeting of the American Society of Clinical Pathologists, 2011.
Welch, S. Hemoglobinopathies and Thalassemias. Clinical Lab News.Oct 2009, Vol 15.
Georgia Newborn Screening Manual for Metabolic Diseases and Hemoglobinopathies, pp 38-61.