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Alpha Thalassemia

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Abstract
Group of hemoglobin synthesis disorder caused by mutations or deletions in at least 1 of the 4 alpha-globin genes, leading to variably impaired alpha-globin chain production, with accumulation of the now excess and unpaired beta-globin chains. Most are asymptomatic, may present with fatigue, dizziness, shortness of breath, jaundice, hypersplenism, symptoms of gallstone, growth retardation in child, mild dysmorphic facial features (Maxillary hypertrophy, frontal bossing, and prominence of malar eminences), and extra medullary hematopoiesis. Antenatal diagnosis (CVS at 10—12 week, amniocentesis, fetal blood sampling after 18 weeks of gestation).

Keywords: hemoglobin, disorder, hypersplenism, Thalassemia

Introduction

Alpha Thalassemia

Definition

Group of hemoglobin synthesis disorder caused by mutations or deletions in at least 1 of the 4 alpha-globin genes, leading to variably impaired alpha-globin chain production, with accumulation of the now excess and unpaired beta-globin chains. [1, 2] Normal human hemoglobin consists of a tetramer of 2 pairs of globin polypeptide chains, 1 pair of alpha-like chains and 1 pair of nonalpha chains, each of which contains a haem group. Two copies of the alpha-globin gene (designated alpha-2 and alpha-1) are located on each chromosome 16 [3].

Epidemiology

It is found in malarial regions of the world (Mediterranean, South-east Asia, and Indian Sub-continent, Middle East, Sub-Saharan Africa) [4, 5].

Types: There are 2 major varieties of alpha-thalassemia:

1. Alpha (0) thalassemia (--/), in which both alpha-globin genes on the same chromosome are deleted
2. Alpha (+) thalassemia (-alpha/), in which 1 of the 2 alpha globin genes on the same chromosome is deleted or mutated.

Classification: 4 different and distinct alpha-thalassemia's:

1. **Silent carrier:** or alpha-thalassemia silent trait or alpha-thalassemia minor. (1 affected alpha-globin gene), asymptomatic and hematological normal.
2. **Alpha-thalassemia trait:** (2 affected alpha-globin genes), either heterozygous (2 on same chromosome) or homozygous (1 gene on each chromosome). Patients may have a mild asymptomatic anemia with a normal mean corpuscular volume (MCV) and slightly low mean corpuscular hemoglobin (MCH), and frequently have jaundice and splenomegaly.
3. **Hb H disease:** (typically 3 affected alpha-globin genes)
4. **Hb Bart hydrops fetalis syndrome:** or Alpha Thalassemia Major (typically deletion of all 4 alpha-globin genes). These infants may survive with intrauterine transfusional support, but are at risk for severe congenital anomalies and severe maternal complications (placentomegaly, hypertension, severe pre-eclampsia, and hemorrhage).

Acquired Hb H disease is rare and occurs in association with hematological disorders, most commonly in male patients with myelodysplastic syndrome.

Rare inherited mutations in either chromosome 16 or the X chromosome (ATR-X syndrome) lead to alpha-thalassemia with associated mental retardation and other abnormalities.

Pathophysiology

Reduced alpha-globin chain synthesis and decreased Hb A (alpha2beta2) leads to the characteristic microcytosis and hypochromic seen with the disease, excess of free non-alpha chains, and formation of gamma 4 (Hb Bart) and beta 4 (Hb H) tetramers. Hemolysis, predominantly extravascular destruction, due to rigid RBC membrane or oxidant injury.

Clinical presentation

Most are asymptomatic. May present with fatigue, dizziness, shortness of breath, jaundice, hypersplenism, symptoms of

gallstone, growth retardation in child, mild dysmorphic facial features (Maxillary hypertrophy, frontal bossing, and prominence of malar eminences), and extramedullary hematopoiesis.
Many patients with Hb H are also clinically well, but are at risk for: acute hemolytic episodes, aplastic crises, iron overload even in the absence of chronic transfusions, hypersplenism, gallstones, leg ulcers, growth retardation and endocrine disorders (hypothyroidism, vitamin D deficiency, osteoporosis, and hypogonadism)

Workup
complete blood count (low Hb, low MCV, low MCH, high RBC) with peripheral smear (Hypochromia, microcytosis, target cells, increased polychromasia, red cell fragments, basophilic stippling), reticulocyte count (increase). If low MCV or MCH check iron profile (serum ferritin, iron, transferrin saturation, TIBC). Hb H is not always reliably detectable by routine hemoglobin electrophoresis, and some experts feel that Hb H inclusion bodies are more reliable for the diagnosis of Hb H disease in high-performance liquid chromatography (HPLC) and DNA-based alpha-globin gene testing. If iron status is significantly elevated as evident by a serum ferritin > 800 ng/ml, hepatic iron overload should be assessed by magnetic resonance imaging (MRI), superconducting quantum interference devices (SQUID), or liver biopsy. (6)

Differential diagnosis
Iron deficiency anemia, beta thalassemia, anemia of chronic disease, hemolytic anemias,

Prevention
Person should investigate further if microcytosis (low MCV <80 fl) or low MCH <27, without iron deficiency anemia and want to conceive such as Hb electrophoresis and DNA testing.

Screening
Antenatal diagnosis (CVS at 10—12 week, amniocentesis, fetal blood sampling after 18 weeks of gestation) and counselling, and new born screening. (7, 8)

Management

Table 1

	Non-Pregnant	Pregnant
Acute hemolysis	Identify cause, monitoring, folic acid supplement, RBC transfusion	Same
Aplastic crisis	RBC transfusion	Same
Silent carrier	Supportive care, avoid iron supplement	Routine antenatal if no iron overload
Thalassemia trait	Supportive care, avoid iron supplement	Routine antenatal if no iron overload
Hb H disease	Supportive care, folic acid supplement Adjunct: Iron chelation, RBC transfusion, splenectomy, Hematopoietic stem cell transplant	Routine antenatal if no iron overload, Adjunct: RBC transfusion if Hb <8 gm/dl
Hydrops fetalis	Maternal support	Maternal support, monitor and manage complications

Iron overload
All patients ≥10 years of age with non-transfusion-dependent thalassemia syndromes (≥15 years in patients with deletional Hb H disease) should have MRI (liver, heart) at 1 to 2 year intervals, serum ferritin levels every 3 months. Start iron chelation therapy if liver iron concentration is ≥5 mg Fe/g dry weight (or serum ferritin level is ≥800 ng/ml). (9, 10)
Folic acid: children and adults: 1 mg orally daily until response, then 0.4 mg orally once daily.

Emerging management
1. Gene therapy
2. Fetal DNA in maternal blood
3. Erythropoiesis stimulating agents

Prognosis
Depend on type of alpha thalassemia. Silent and alpha-thalassemia trait are usually asymptomatic and require only education and appropriate genetic counselling. Hb H disease variable severity, Patients must be educated about complications (Exacerbations of hemolysis, cholelithiasis, ulcers, and growth retardation) and should be monitored for severe anemia and other complications. Hb Bart unlikely event that they survive, such patients will require lifelong red cell transfusional support, with the attendant requirement for iron chelation. Such patients have rarely been reported to successfully undergo hematopoietic stem cell transplantation.

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