

Alpha Thalassemia – A Rare but Perilous Blood Disorder

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ABSTRACT

The α -thalassemias are the most common inherited disorders of hemoglobin (Hb) synthesis due to deletions or point mutations. Alpha globin is made by four genes, two on each strand of chromosome 16. Individuals who have one or two abnormal alpha globin genes have alpha thalassemia trait. It is commonly found in Africa, the Middle East, India, Southeast Asia, southern China, and occasionally the Mediterranean region. When a person has only one functional alpha globin gene, they have Haemoglobin H disease, require regular medical care and may experience lifelong anaemia of mild to moderate degree. When a person has no alpha globin genes, they have a severe condition called Hb Bart's hydrops fetalis. It affects a foetus long before birth, resulting in death during pregnancy or shortly after birth. Those with Haemoglobin H disease may require blood transfusions to correct anaemia. There is no treatment or cure for Hb Bart's hydrops fetalis.

Key words: α -thalassemias; Haemoglobin H disease; Hb Bart's hydrops fetalis; blood transfusions

INTRODUCTION

The generic term α thalassaemia encompasses all of those conditions in which there is a deficit in the production of α globin chains of haemoglobin (Hb).¹ It is caused by deletions of variable length or point mutations in one or both α -globin genes.² The α -thalassemias are the most common inherited disorders of hemoglobin (Hb) synthesis due to deletions or point mutations affecting 1 or more α -globin genes leading to decreased or absent α -globin chain synthesis. In Hb Bart's hydrops fetalis, there is no functional α gene and results in fetal death at or around the time of birth. Hb H disease is the most severe form of α -thalassemia.

EPIDEMIOLOGY

Like all common globin gene disorders (sickle cell trait and β thalassaemia) α thalassaemia occurs at high frequencies

throughout all tropical and subtropical regions of the world.⁴ Alpha thalassemia is common throughout parts of the world where malaria is endemic. Multiple studies have suggested that the presence of both single and double α -globin gene deletions confer a protective effect from malaria. Listed below are the approximate prevalence percentages of various populations with some forms of alpha thalassemia:

- Europe – 4–12%
- Middle East and western Asia – 12–55%
- Southeast Asia – 6–75%
- Africa – 11–50%
- South America and the Caribbean – 7%⁵

Most of the available data in India on α -thalassaemia are based on cord blood screening for the presence of Hb Bart's. A varied prevalence of α -thalassaemia ranging from 1% to 18% has been reported in the general Indian population.⁶⁻⁷ In India, there have been sporadic reports of alpha thalassaemia. Some cases of Hb-H disease have been found in West Bengal⁸ and screening of newborns in West Bengal and Mumbai showed that 2% and 4% of cord bloods contained Hb Barts.⁹⁻¹⁰ Using gene mapping analysis, alpha thalassaemia has been diagnosed in a high proportion of a tribal (Toda) population in South India¹¹ and in East India.¹² The prevalence of alpha-thalassaemia in India varies from one sub-geographical area to another.¹³

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CLINICAL DESCRIPTION

Alpha-thalassemia (α -thalassemia) has two clinically significant forms:

Hemoglobin Bart hydrops fetalis (Hb Bart) syndrome, the most severe form of α -thalassemia, is characterized by fetal onset of generalized edema, ascites, pleural and pericardial effusions, and severe hypochromic anemia, in the absence of ABO or Rh blood group incompatibility. It is usually detected by ultrasonography at 22 to 28 weeks' gestation and can be suspected in an at-risk pregnancy at 13 to 14 weeks' gestation when increased nuchal thickness, possible placental thickness, and increased cardiothoracic ratio are present. Death in the neonatal period is almost inevitable. All four α -globin alleles are deleted or dysfunctional (inactivated).¹⁴

Hemoglobin H (HbH) disease should be suspected in an infant or child with a mild-to-moderate (rarely severe) microcytic hypochromic hemolytic anemia and hepatosplenomegaly. Mild thalassemia-like bone changes are present in approximately one-third of affected individuals. Unlike Hb Bart syndrome, HbH disease is compatible with survival into adulthood. HbH disease is a result of deletion or dysfunction of three of four α -globin alleles.

Alpha-thalassemia also has two carrier states:

Alpha⁰-thalassemia generally results from deletion or dysfunction of two α -globin genes in *cis* ($-\alpha/\alpha$).

Alpha⁺-thalassemia usually results from deletion or dysfunction of one α -globin gene. Homozygosity for α^+ thalassemia results in an α -thalassemia trait hematologic phenotype.¹⁵

DIAGNOSIS

Initial laboratory testing should include a complete blood count with red cell indices, HPLC or Hb electrophoresis and eventually α/β -globin chain synthesis ratio measurement. The latter procedure, however, is sometimes bypassed by DNA analysis as a less complicated method to diagnose α -thalassaemia.¹⁶

Alpha thalassaemia is most frequently suspected initially on the basis of a routine full blood count. All affected individuals have a variable degree of anaemia (Hb), reduced mean corpuscular haemoglobin (MCH/pg),

reduced mean corpuscular volume (MCV/fl) and a normal or slightly reduced level of the minor HbA2.¹⁷

α -THALASSEMIA

Alpha-Thalassemia occurs when a genetic mutation leads to reduced synthesis from one or more of the four α -globin genes.¹⁸ α^0 -Thalassemia refers to a deletion of both α globin genes on the same chromosome (designated $-/$), while α^+ -thalassemia refers to a deletion of a single α globin gene, leaving the other α globin gene on that chromosome intact (i.e., $\alpha^-/$). In the large majority of cases of α -thalassemia, the α globin chains are structurally normal: they are merely reduced in quantity.

Individuals with only one α globin deletion, that is, heterozygotes for α^+ -thalassemia, are known as silent carriers ($-\alpha/\alpha$, $-\alpha^-/\alpha$). These individuals are asymptomatic and generally have normal routine hematologic findings: a CBC will usually show normal Hb, MCV, and MCH. Rarely the MCV and/or MCH can be low. Routine laboratory testing for thalassemia (such as Hb electrophoresis, Hb HPLC, and H body staining of a peripheral blood smear) is usually negative outside the newborn period. In general, diagnosis of single gene deletion α -thalassemia can be proven only by molecular (DNA) testing.¹⁹

TREATMENT AND PROGNOSIS OF SURVIVING INFANTS

Alpha thalassemia trait

Carriers of α^+ -or α^0 -thalassaemia alleles generally do not need treatment, because their anaemia is either very mild or absent due to a compensating high red blood cell count.

HbH disease:

The type of mutation influences the clinical severity of HbH disease. The most common form is the deletion type, which causes a milder form of HbH disease. These patients may require intermittent transfusion therapy especially during intercurrent illness. Chronic transfusion therapy is very uncommonly required in this group. However, patients with non-deletional types of HbH disease may have moderately severe splenomegaly and require more regular transfusion and ultimately splenectomy.²⁰⁻²² Iron overload is uncommon in HbH disease patients (compared with β thalassaemia) but has been recorded in older patients (>45 years) and those treated with regular blood transfusion.

Hb Bart's Hydrops Foetalis Syndrome

Most pregnancies in which the foetus is known to have the Bart's hydrops foetalis syndrome are terminated. In a very small number of cases intra-uterine transfusions following early detection of homozygous α^0 -thalassaemia have resulted in the birth of non-hydrotic infants, some without significant neurological or congenital abnormalities, however, most survivors experience a stormy perinatal course and a high prevalence of congenital urogenital and limb defects.^{23–28}

For the Pregnant Woman

With very rare exceptions, all fetuses with the Hb Bart's hydrops foetalis syndrome succumb to severe fetal hypoxia in utero during the third trimester of gestation or within hours after birth.^{29–31} The health care measures to combat this inevitably fatal disorder should be aimed at identifying couples at risk in order to provide them with timely counseling, and prenatal diagnosis during early pregnancy.

In Utero Hemopoietic Stem Cell Transplantation

Intrauterine hemopoietic stem cell transplantation has been proposed as another treatment alternative.³²

CONCLUSION

Prevention and awareness programmes with early detection, timely genetic counseling and the availability of prenatal diagnosis during early pregnancy are essential to check the birth of thalassaemic child. These programmes and strategies are important for many couples who are at risk so that they will be spared of serious medical and psychological ordeals in their quest for having families with children. It is therefore crucial that this genetic disorder is recognized, so that the appropriate maternal health care and preventive measures can be provided to the affected couples and communities.

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