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Alpha Thalassemia Disorders

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1. Introduction

1.1 Alpha thalassaemia and new developments

The thalassaemias, the commonest monogenic diseases, are a family of inherited disorders of haemoglobin synthesis characterised by a reduced output of one or other of the globin chains of adult haemoglobin. They are likely to pose an increasing health problem for many developing countries during the early part of the new millennium (1). This review focuses mainly on their control and management, a subject of increasing importance not only for parts of the world in which the disease is particularly common but for any country which has an immigrant population from these regions.

1.2 Genetic control of haemoglobin

All the human haemoglobins consist of two different pairs of globin chains combined with haemoglobin, the iron containing moiety that binds oxygen. Fetal haemoglobin, the synthesis of which continues throughout fetal life and declines after birth, has alpha 2-gama 2, and in adults there is a major component called haemoglobin A (alpha 2-beta 2) and a minor fraction, haemoglobin A2.

The sequence of DNA that comprises the globin genes and the chromosomal regions around them has been determined. Each gene consists of three coding regions (exons) and two non-coding regions (introns). When a globin gene is transcribed, a mirror image molecule called messenger RNA is copied from one of the strands of DNA of the particular gene. While it is still in the nucleus of the red cell precursor, the intron sequences are removed and the exon sequences spliced together in the correct order to form the template for the production of a globin chain. This processed molecule moves into the cytoplasm, where it acts as the blueprint whereby appropriate amino acids are strung together to form a definitive globin chain. In adult red cells alpha and beta chains synthesised in this way combine with haem to form definitive haemoglobin molecules. There are also critical regulatory regions of DNA that are involved in ensuring that globin chains are produced in appropriate amounts in the correct tissues at the right time of development. The thalassaemias result from mutations or gene deletions that involve one or other of these complex steps.

1.3 Definitions and classification

The alpha and beta thalassaemias are by far the most important. In many populations in which thalassaemia is common, the genes for structural haemoglobin variants such as

haemoglobins S, C, and E are also common, so it is not unusual for individuals to inherit a gene for thalassaemia from one parent and that for a haemoglobin variant from the other. The most important diseases of this type are sickle cell thalassaemia and haemoglobin E thalassaemia. Most of the important forms of thalassaemia are inherited in a Mendelian recessive fashion; carrier parents who are symptomless have a one in four chance of having a severely affected child.

1.4 Population distribution

The thalassaemias are distributed across the Mediterranean region, the Middle East, the Indian subcontinent, and throughout southeast Asia. In many of these countries gene frequencies for the different thalassaemias and structural haemoglobin variants are excess of alpha globin chains that are produced, and a genetically determined ability to produce high levels of fetal haemoglobin, are important factors (2). Heterozygotes for beta thalassaemia have mild hypochromic anaemia with small red cells and a raised concentration of haemoglobin A2.

2. Epidemiology

Like all common globin gene disorders (sickle cell trait and β thalassaemia) alpha thalassaemia occurs at high frequencies throughout all tropical and subtropical regions of the world. In some areas, the carrier frequency of alpha thalassaemia may be as high as 80-90% of the population, almost at fixation (3-7). It is thought that all of these globin gene disorders (including alpha thalassaemia) have been selected because in some way they protect carriers from the ravages of falciparum malaria. The micro epidemiological evidence supporting this is very strong (8, 9). The mechanisms underlying this protection have been extensively studied but remain unknown. Of all globin disorders, alpha thalassaemia is the most widely distributed and therefore many individuals in these areas have interacting combinations of these variants (e.g. both alpha and β thalassaemia). Due to differences in the interactions between the various molecular defects underlying alpha thalassaemia HbH disease is predominantly seen in South East Asia, the Middle East and the Mediterranean. In passing it should be mentioned that ATR16, ATR-X and ATMDS syndromes show no geographical bias in their distributions.

Although the previously established distribution of alpha thalassaemia, over the past few decades there have been massive population movements so that now the globin gene disorders, thought to be rarities in North European and North American clinical practice, have become major diagnostic and therapeutic challenges for our current health care systems (10).

2.1 Screening and prevention

The carrier states for all the important thalassaemias can be identified (11, 12) and methods for their prenatal diagnosis are well established. Where this approach is acceptable to families on religious and other grounds it is being adopted as a way of controlling thalassaemia. Control programmes require screening, either at the population level if the disease is particularly common or, more usually, at the first visit to the antenatal clinic. Every woman of appropriate racial background should be screened for thalassaemia by a

standard blood count with particular reference to the red cell indices. All the important carrier states for the different forms of thalassaemia are associated with a reduced mean cell haemoglobin concentration and cell volume. When a blood picture of this kind is encountered it should be followed by the estimation of the haemoglobin A2 concentration, which is raised in all the common forms of beta thalassaemia. It is important therefore to obtain the help of an expert laboratory to distinguish between these possibilities. If a mother is a carrier for alpha thalassaemia her pregnancy is at risk for the Bart's hydrops fetalis syndrome, whereas the worst possible outcome of a pregnancy involving a woman homozygous for alpha thalassaemia is the much milder condition, haemoglobin H disease. The forms of beta thalassaemia with normal haemoglobin A2 concentrations may interact with the other thalassaemia genes to produce a severe phenotype.

Once a woman has been diagnosed as a carrier for one or other forms of thalassaemia her partner should be tested and the couple referred for expert genetic counselling. If they opt for prenatal diagnosis they should be referred as early as possible.

Early prenatal diagnosis, first by fetal blood sampling and later by chorion villus biopsy and direct analysis of the globin genes, is now extremely effective (13). The error rate in experienced centres is now well under 1%, most of the mistakes resulting from either contamination of the fetal DNA by maternal tissue, nonpaternity, or technical problems of DNA analysis (14).

Alpha thalassaemias (15, 16) show several important differences from beta thalassaemia. Because alpha chains are shared by fetal and adult haemoglobin the disease is manifest in both fetal and adult life. Furthermore, excess gama and beta chains do not precipitate immediately in the bone marrow like alpha chains but produce the physiologically useless and unstable tetramers: haemoglobin Bart's and haemoglobin H. Since the alpha genes are duplicated the genetics of alpha thalassaemia is more complicated than that of beta thalassaemia. Usually these alpha genes are lost by deletion, though sometimes they are inactivated by a point mutation, as is the case in the beta thalassaemias.

The homozygous state for alpha thalassaemia produces intrauterine death with a profoundly anaemic and hydropic fetus: the haemoglobin Bart's hydrops fetalis syndrome. Mothers carrying babies of this type commonly have toxaemia of pregnancy and post partum bleeding.

Alpha thalassaemia is certainly not a rare genetic trait. On the contrary, it is one of the most common human genetic abnormalities known. Carriers of alpha thalassaemia are found at polymorphic frequency (>1%) in all tropical and subtropical populations that have been studied and, in some areas, the carrier state has almost gone to fixation. This is because carriers of alpha thalassaemia are thought to be at a selective advantage in areas where falciparum malaria is or has been endemic. In areas where the carrier state is common, two clinically important diseases (HbH disease and Hb Bart's hydrops foetalis) occur in compound heterozygotes and homozygotes. The reason for discussing this here is therefore not because these diseases are rare, rather that they may be rarely considered by physicians outside of the regions where thalassaemia commonly occurs. For example, a retrospective study of obstetric records in the U.K. by Petrou et al. revealed an underdiagnosis of both alpha-thalassaemia trait and alpha-thalassaemia hydrops foetalis (17).

With the massive migrations that have occurred over the past few decades it is important to bring these rarely considered diseases to the general attention of clinicians in Northern Europe and North America.

2.2 Disease names and synonyms

The generic term alpha thalassaemia encompasses all of those conditions in which there is a deficit in the production of the alpha globin chains of haemoglobin (Hb) which is a tetrameric molecule including two alpha-like and two β-like globin chains (alpha2β2). Underproduction of alpha globin chains gives rise to excess β-like globin chains which form γ4 tetramers, called Hb Bart's (in foetal life) and β4 tetramers, called HbH (in adult life). Individuals who carry mutations affecting the alpha globin genes on one chromosome, associated with minimal anaemia, are said to have alpha thalassaemia trait. Compound heterozygotes and some homozygotes for alpha thalassaemia have a moderately severe anaemia characterised by the presence of HbH in the peripheral blood. This condition is referred to as HbH disease. Finally some individuals who make very little or no alpha globin chains have a very severe form of anaemia which, if untreated, causes death in the neonatal period. This condition is called the Hb Bart's hydrops foetalis syndrome (18-21).

Rarely patients have been seen with very large deletions which remove the alpha globin genes but also remove many other genes that surround them. This condition is associated with developmental abnormalities (including intellectual disability) and is referred to as the alpha thalassaemia/mental retardation syndrome on chromosome 16 (ATR16 syndrome: OMIM:141750, reviewed in Higgs et al., 2009 (22) and Wilkie et al., 1990 (23)). Also patients with a rare form of syndromal X-linked mental retardation associated with alpha thalassaemia have been described, in which the intellectual disability is more severe and the dysmorphic features show striking similarities among patients. This rare condition is called ATR-X syndrome and has been found to involve mutations in a chromatin associated protein called ATRX on the X-chromosome (ATR-X syndrome: OMIM:301040, reviewed elsewhere)(22, 24-27).

Finally, an acquired form of alpha-thalassaemia referred to as the ATMDS syndrome has been described. This predominantly occurs in elderly males with a pre-malignant, clonal haematopoietic disease called myelodysplasia (MDS). This rare syndrome involves acquired mutations in the ATRX gene causing alpha thalassaemia (OMIM:300448, reviewed in Gibbons et al., 2003;Higgs et al., 2009) (22, 28). Since these rare conditions have all been reviewed elsewhere they will not be discussed further in this synopsis.

2.3 Definition/diagnostic criteria

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. These parameters are discussed in greater detail below. When the level of alpha globin synthesis falls below ~70% of normal, in the foetal period, excess γ globin chains form Hb Bart's which can be detected on routine Hb analysis (29-35). In adult life, excess β globin chains form β4 tetramers of HbH in the cell and

these can be identified by staining the peripheral blood with 1% brilliant cresyl blue (BCB) (36-38), or when present in sufficient quantity by routine Hb analysis (36, 39). Previously alpha thalassaemia was confirmed by globin chain biosynthesis, when the alpha/β globin chain biosynthesis ratio was reduced to less than ~0.8 (40-44).

All of these parameters are reduced in alpha thalassaemia but none of them alone or in combination can accurately or consistently predict the genotype for which directed molecular analysis of the alpha globin cluster is required and this is discussed below.

2.4 Clinical description

The clinical phenotypes of most individuals with alpha thalassaemia are very mild and may not be noticed during life other than when a routine full blood count is examined. Patients with HbH disease have a variable phenotype and those with Hb Bart's hydrops foetalis have a lethal form of anaemia.

2.5 Alpha thalassaemia trait

Apart from mild to moderate microcytic hypochromic anaemia (detected on a routine blood count), carriers (heterozygotes) of alpha thalassaemia, whatever the molecular basis (see below), are clinically asymptomatic and the diagnosis (when made) is often established during a regular health check or during antenatal screening. Complaints related to more severe anaemias, such as fatigue, listlessness and shortness of breath are uncommon and almost certainly related to other concomitant disorders.

Carriers of alpha^{+}- or alpha^{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. On the other hand, once a diagnosis of alpha thalassaemia trait is made, there is a tendency to discard iron-deficiency as a subsequent cause of anaemia. Carriers of alpha thalassaemia can be anaemic as a consequence of coexisting nutritional deficiencies, such as iron deficiency, folate or vitamin B12 deficiencies and should be managed correctly from this point of view. Of course prophylactic iron should never be given to carriers of alpha thalassaemia who are at risk of developing iron overload if treated inappropriately.

2.6 Genotype/phenotype correlations

Although there are now 128 different molecular defects known to cause alpha thalassaemia and an ever increasing number of potential interactions, the clinical phenotypes (broadly classified as alpha thalassaemia trait, HbH disease and Hb Bart's hydrops foetalis) resulting from the interactions between these various molecular defects. The severity of the clinical phenotype correlates very well with the degree of alpha globin chain deficiency. An important additional point is that, in general, interactions involving non-deletional forms of alpha^{+}-thalassaemia result in a more severe phenotype than in those with deletional forms of alpha^{+}-thalassaemia (45-59).

2.7 Diagnosis and diagnostic methods

Initial laboratory testing should include a complete blood count with red cell indices, HPLC or Hb electrophoresis and eventually alpha/β-globin chain synthesis ratio measurement.

The latter procedure, however, is sometimes by passed by DNA analysis as a less complicated method to diagnose alpha-thalassaemia.

2.8 Molecular analysis

Over the past 30 years it has become increasingly possible to diagnose alpha thalassaemia accurately and define the precise defects underlying these disorders using a variety of molecular genetic approaches. Ultimately, most alpha globin rearrangements have been characterised by Southern blotting and DNA sequence analysis. However, for today's diagnostic demands these techniques are far too laborious to apply in each case, and from the original work defining these mutations, rapid screening assays have been developed.

2.9 Differential diagnosis

Sometimes carriers of alpha$^+$-thalassaemia present with normal haematology, especially carriers of –alpha 3.7 and non deletional mutations affecting the alpha1-gene. Such individuals may be normocytic or borderline hypochromic without anaemia. These can only be found by chance during routine molecular analysis for haemoglobinopathies.

2.10 Prognosis

There is no reason to think that carriers for alpha thalassaemia have any altered prognosis for life compared to the normal population. The prognosis for patients with HbH disease who are newly emerging in previously nonendemic countries, like Northern Europe and Northern America, is less clear. Anecdotally many patients with HbH disease appear to lead a normal life in all respects. Some even remain undiagnosed throughout their lives. However, detailed actuarial studies are not available. When complications arise, of course the outcome depends on the awareness and availability of health care systems. Certainly some complications suffered by patients with HbH disease are life threatening in the absence of adequate medical care (21, 60, 61). A long term problem for all patients with HbH disease is the unwanted accumulation of iron which may be more of a problem for those with severe HbH disease with nondeletional alpha- thalassaemia (62, 63).

Clearly, previously undiagnosed and untreated infants with the Hb Bart's hydrops foetalis syndrome die in the perinatal period. The recent attempts to rescue infants with this syndrome either by intra-uterine transfusion or by transfusion in the perinatal period have met with variable success. As discussed above many infants develop other irreversible abnormalities during foetal life and even with rescue the infant will be required, either to receive lifelong blood transfusion and iron chelation therapy, or bone marrow transplantation with its attendant risks.

3. Therapy and management of Alpha-thalassemia

Alpha-thalassemia silent carrier and alpha-thalassemia trait:

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. An individual with one abnormal alpha globin gene is said to be a silent carrier of alpha thalassemia. This condition, in

which one of the four alpha globin genes is missing or defective, generally causes no health problems because the lack of alpha globin protein is so small that there is no anemia. It is called "silent carrier" because of how difficult it is to detect. Silent carrier state is "diagnosed" by deduction when an apparently normal individual has a child with hemoglobin H disease or alpha thalassemia minor. It can also be diagnosed by special DNA testing.

Hb H disease:

Hemoglobin H disease is an inherited hemoglobin disorder in which three of the four alpha globin genes normally present are deleted or have a mutation which impairs alpha globin chain production. This leads to an excess of beta globin chains, which are unstable, precipitate within the cell and lead to destruction of the red blood cells. Hemoglobin H is a thalassemia-like syndrome characterized by hemolysis as well as ineffective red cell production. Co-inheritance of HbH with other globin gene defects can affect the severity of the condition. Hemoglobin H disease has a wide spectrum of clinical severity in patients, therefore, early diagnosis is important so patients can be followed. Hemoglobin levels and the patient's growth and development should be regularly monitored. Complications related to chronic hemolysis also need to be assessed. Infections should to be monitored closely so any severe drop in hemoglobin can be recognized and treated. Health care monitoring and maintenance with appropriate immunizations are important as well.

Hb Bart hydrops fetalis:

Hydrops fetalis is a serious disorder, usually indicative of an ominous prognosis for the affected fetus. There are many causes, including both hereditary and acquired diseases. With population migrations during the past decades, this syndrome is now seen in increasing numbers in other parts of the world. Hydrops fetalis can be diagnosed and monitored by ultrasound scans. Prenatal ultrasound scanning enables early recognition of hydrops fetalis and has been enhanced with the introduction of MCA Doppler. Recent advances in molecular genetics have provided insights into the mutations and pathophysiology causing α-thalassemias, as well as definitive clinical diagnostic tests for adult carrier detection and prenatal diagnosis. Severely anemic fetuses can be treated with blood transfusions while still in the womb.

4. Future expectations in Alpha thalassaemia

Alpha thalassemia severity ranges from asymptomatic to fatal in utero. Hemoglobin H disease, a mutation of three alpha globin genes, is more severe than previously recognized. New developments in the epidemiology, treatment and prognosis of thalassemia have dramatically altered the approach to the care of affected patients, and these developments are likely to have an even greater impact in the next few years. Alpha thalassemia is being recognized with increasing frequency in Turkey, and newborn screening for Hemoglobin Barts in some states is leading to early detection of Hb H disease. New data clarify the importance of distinguishing these two disorders because of the increased severity associated with Hb H. The use of intrauterine transfusions to sustain the viability of fetuses with homozygous alpha thalassemia has created a new population of patients with severe thalassemia and has raised new and complex issues in genetic counseling for parents with alpha thalassemia trait. Demographic changes have required an awareness and

understanding of the unique features of alpha thalassemia disorders that were previously uncommon in Turkey but are now seen more frequently in children and recognized more consistently in adults. Anemia, hypersplenism, hemosiderosis, growth failure, and osteoporosis are commonly noted as the patient ages. Alpha thalassemia major, a usually fatal in utero disease, is now recognized to have a complex molecular and phenotypic expression with increasing births being reported. Surviving newborns without intrauterine transfusion often have congenital anomalies and neurocognitive injury. Serious maternal complications often accompany pregnancy. Doppler ultrasonography with intrauterine transfusion ameliorates these complications. The high incidence in many populations mandates population screening and prenatal diagnosis of at-risk couples. Universal newborn screening has been adopted in several regions with DNA confirmatory testing. These advances have resulted in ethical dilemmas for the family and the provider.

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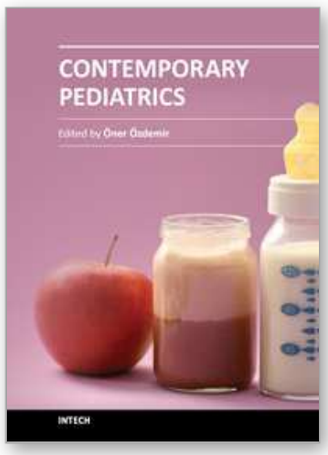

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