MORPHOLOGIC PICTURE OF WHITE BLOOD CORPUSCLE SERIES IN THALASSAEMIC SYNDROMES

THESIS

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BY

MOHSEN SALEH EL-ALFY

M.B, B.Ch.

AIN SHAMS UNIVERSITY, FACULTY OF MEDICINE

SUPERVISOR:

Professor Dr. NEMAT HASHEM

HEAD OF PEDIATRICS AND GENETIC SECTIONS, FACULTY OF MEDICINE, AIN SHAMS UNIVERSITY.

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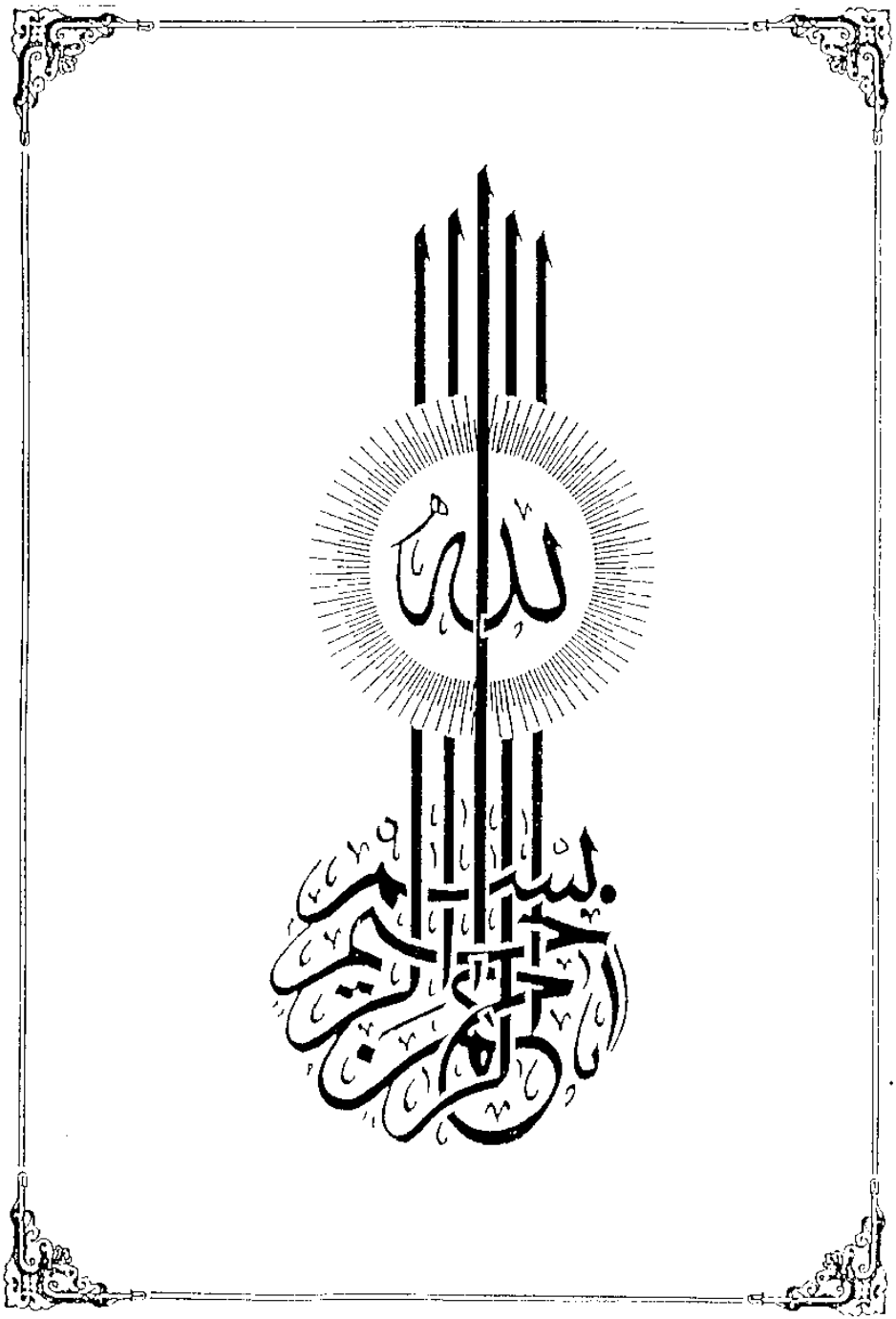

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AIM OF WORK

Thalassaemic syndromes are the commonest genetically determined chronic haemolytic anaemia encountered in Egypt. As a result of the chronic haemolytic process, bone marrow and reticuloendothelial system over-stimulation may result in emergence of premature forms of white blood corpuscles in peripheral blood.

The incidence of malignant transformation of myeloid series of such cases of chronic haemolytic anaemia has not yet been fully explored.

This work therefore aims at testing the morphological changes in white blood series in peripheral blood and bone marrow as indicated in Egyptian B-thalassaemic patients.

HISTORICAL REVIEW:

The stody of how the present state of knowledge about thalassaemia was realized falls into four phases. Between 1925 and 1940 the first descriptions of the clinical features of the homozygous and heterozygous thalassaemic syndromes for different types of thalassaemia was recorded.

In 1925, Cooley and Lee described five children with anaemia, hepatosplenomegaly, pigmentation of skin, thickening of long bones, skull, decreased red cell osmotic fragility and leucocytosis. Caminopetros(1938) put the first suggestion that thalassaemia is a genetic disorder.

In the period from 1940 to 1950 the true genetic basis of the disorder was recognised and there was an amalgamation of information from Europe and the United STates which gave a clearer picture of the inheritence of the syndrome. In 1946 Vecchio and Rick in 1952 suggested that thalassaemia results from a defect in haemoglobin A synthesis with persistent production of haemoglobin F.

By 1960 it has become obvious that thalassaemia is, in fact, a very diverse group of genetic disorders which result from abnormalities of haemoglobin synthesis.

Since 1960 steady progress has been made in elucidating the biochemical nature of the thalassaemia disorders, to the extent that the defect in some of them has now been pinopointed at the molecular level (Weatherall and Clegg 1981).

Recently Hashem N. (1981) has been studying the genotypes of B and ∝ thalassaemia syndromes prevalent among Egyptians.

PREVALANCE AND GEOGRAPHIC DISTRIBUTION:

The thalassaemias are found in a broad belt extending from the Mediterranean basin to India and the Far East (Keberle H. 1964).

The B-thalassaemia gene is particularly prevalent in Italy and Greece (Chatterjea JB.1966). In North America, thalassaemia is noted primarly in persons of Italian and Greek descent. The B-thalassaemia gene is prevalent in the area around the Mediterranean sea. The thalassaemia trait occurs with a relatively low prevalance among the indigenous population of North Africa - for instance at about 3 % in Algeria, Morocco, Tunisia, probably Libya and Egypt. It may be much more common in some parts of Egypt (Modell, B.1982). The B-Thalassaemia is the most common chronic haemolytic anaemia in Egypt (Sabri 1973).

NORMAL HUMAN HAEMOGLOBINS:

The haemoglobin molecule is a tetramere, i.e., it is made up of 2 pairs of polypeptide chains, each chain having a haeme group attached to it.

The human haemoglobins undergo differential maturation within the red cells of the embryo, fetus, child and adult. They are classified as: Embryonic haemoglobins. The Gower haemoglobins $\zeta_2 \epsilon_2$ and $\alpha_2 \epsilon_2$ predominate in embryos 4 to 8 weeks gestation, but by the 3rd,month they have disappeared. Fetal Haemoglobin. It predominates after 8th gestational week and in the 6th,month old fetus it constitutes 90 percent of the total haemoglobin. At bith haemoglobin F averages 70 percent of the total. A trace is detected by the age of 6 to 12 months. Haemoglobin F contains gamma chains which substitute for beta chains of Hgb A and represents as $\alpha^A_2 \gamma^F_2$. Adult haemoglobins: Hgb A can be detected as early as 16 to 20 weeks of gestation. By the 6th,month of gestation, there is about 5 to 10 percent of Hgb A present. At term Hgb A averages 30 percent. By 6 to 12 months of age the normal adult Hgb pattern appears. It is represented as $\alpha^A_2 B^A_2$. The minor adult Hgb A_2 represented as $\alpha^A_2 \delta^A_2$ accounts for 2.0 to 3.4 percent by 12 months of age.

GENETIC MECHANISMS AND MOLECULAR PATHOLOGY

The molecular basis of the thalassaemia syndromes is highly heterogenous. In some cases globin structural gene deletion have been demonstrated, whereas in others, gene loss has occurred as a result of unequal crossover. Yet other thalassaemia syndromes result from defective transcription and metabolism of globin messenger RNA or from nucleotide mutations producing errors in globin chain termination. For many of the syndromes, the molecular pathology has yet to be defined. Not surprisingly, a similar clinical syndrome can result from several different genotypes producing different molecular aberrations, (Orkin SH.Nathan 1976, Forget BG 1979 and Bark A et al,1980).

- In α-Thalassaemia

In each of the syndromes of α-thalassaemia there is deficiency of α-globin chain synthesis as a result of deficient mRNA. In homozygous α-thalassaemia there is no α-globin m RNA detected while in Hb H disease no more than 10 to 30% of the mRNA is present (Natta Cl et al, 1976 and Ramirez et al, 1976).

Deficient α-globin mRNA, in turn, is most commonly the result of deletions of one or more of the α-globin structural genes (Orkin SH et al,1979).

- In B-Thalassaemia

The B-thalassaemias, like the α-thalassaemias, are due to regulatory mutations resulting in diminished production of a structurally normal globin. In contrast to α-thalassaemias, the B- thalassaemia syndromes appear not to be due to loss of the genes responsible for B-chain synthesis. Despite the heterogenecity of molecular mechanisms, all forms of B-thalassaemia have in common a reduction in either the amount or the functional capacity of the m RNA that codes for B-globin chains. The major variants of B-thalassemia and their molecular defects are summarized in Table N°"I". Study of globin chain synthesis in the homozygous state reveals two major types of B-thalassaemia, one with some residual B-chains (B^{+}type) and another with no B-chains (B°type) (Benz Ej Jr. 1976).

Table N°"I": Molecular Defects in B-thalassemia syndromes

Thalassaemia syndromes	B-Globin synthesis	B-mRNA	B-Globin Gene	δ-Globin synthesis	γ-Globin synthesis
B^+-Thalassaemia	Decreased	Decreased	Present	Present	Present
B^0-Thalassaemia	Absent	Absent	Present	Present	Present
	Absent	Decreased	Present	Present	Present
δB-Thalassaemia	Absent	Absent	Deleted	Absent	Increased
HPFH	Absent	Absent	Deleted	Absent	Increased

A. B^+-Thalassaemia

In B^+-thalassaemia which is the most common type of all B-thalassaemia varities, B-globin synthesis is reduced to 5 to 30% of normal. The deficit in B-globin synthesis; closely parallels a deficit of B-globin m-RNA (Housman D et al, 1973 and Kacian DL et al, (1973).

The small amount of B-globin m-RNA present functions normally as a template for protein synthesis in cell-free systems (Benz EjJr.Forget BG.1971).

B. B^0 Thalassaemia

In homozygous B^0-thalassaemia there is total absence of B-chain synthesis without modification of δ-chain

synthesis. As in B^+-thalassaemia, the immediate basis for the synthetic defect is an aberrant B-mRNA. At least three types of mRNA abnormalities have been identified. Approximately half of those studied have marked deficiency or total absence of B-globin mRNA (Godet J et al,1977, Benz et al 1978 and Old JM et al, 1978).

- In δB-Thalassaemia

In homozygotes for B-thalassaemia, there is no synthesis of either δ-or B-globin chains. Fetal hemoglobin is the only hemoglobin produced. Hence, NO B-or B-like mRNA is detected (Ramirez F et al, 1975).

- In Hereditary Persistence of Fetal Hemoglobin (HPFH)

As in δB-thalassaemia, there is total absence of δ-and B-chain synthesis in HPFH. Unlike δB-thalassaemia, HPFH is characterized by a compensatory increase in γ-Chain synthesis sufficient to bind almost all α-chain synthesis, (Charache S et al 1976 and Forget BG et al 1976)

- In Hb Lepore

The Lepore haemoglobins contain amino acid sequences

corresponding to two different non- α chains. In Hb Lepore, the non- α chain is composed of δ-globin at the amino end and B-globin at the carboxyl end. At least three different types of lepore haemoglobins have been identified in which the site of cross over between the δ-and B-blobin chains is different (Weatherall DJ, Clegg JB 1972 and Benz Ej, Forget BG 1975).

PATHOPHYSIOLOGY

Selective deficiency of one or more polypeptide chains has two immediate consequences: decreased haemoglobin synthesis and imbalance between α-and non-α-chain production. The former is a major determinant of red cell hypochromia, but a more devastating effect is the biosynthetic disruption of globin balance. In the absence of complementary globin chain with which to bind, chains whose synthesis is normal form aggregates, precipitate within the cytoplasm, damage cell membranes, and lead to premature cell destruction, (Weatherall et al 1969 and Nâthan DG, Benz Ej 1976.)

In α-thalassemia, the defect in α-chain synthesis results in an accumulation of γ-chains in the fetal and neonatal period and B-chains thereafter. They are easily oxidized and tend to precipitate with cell aging (Steinberg MH et al, 1976).

In homozygous B-thalassemia, deficiency of B-chain synthesis results in an acummulation of α-chains, (Yataganas X, Fessas P 1972 and Wickramsinghe SN et al, 1973).