STUDIES ON FOETAL HAEMOGLOBIN IN NORMAL EGYPTIAN INFANTS AND CHILDREN AND ON THOSE SUFFERING FROM VARIOUS CONDITIONS OF PHYSICAL AND/OR MENTAL RETARDATION

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By

MAHMOUD SHAFIK ABD EL RAZIK

Under the supervision of :

- Professor S. Awaad, Professor of Pediatrics.
- Professor A. Fahmi, Prof. of Clinical Pathology.
- Assistant Professor M. Essawy.

Ain Shams University, Cairo.

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Foetal Haemoglobin in normal Egyptian infants & children and in some cases of physical and/or mental retardation .

اسم صاحب الرسالة

محمود شفيق عبد الرازق

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C O N T E N T S

INTRODUCTION

The change from foetal to adult erythropoiesis as reflected in peripheral blood has been followed up in many previous studies. It was found that before the age of 32 weeks chemically estimated foetal haemoglobin has reached the adult level. An explanation was offered in terms of progressive maturation of gene controlled enzyme systems; whereby production of gamma chain characteristic of foetal haemoglobin was superseded by that of beta chain of adult haemoglobin.

However, after early infancy foetal haemoglobin can be found in peripheral blood in a variety of conditions, viz :

1. In the presence of clearly inherited abnormality of a high foetal haemoglobin gene "F gene" (Conely, Weatherall and Charachel 1963) (29).
2. In certain non specific anaemias that begin in early infancy.
3. In severe acquired disturbances of haemopoiesis as leukaemia, aplasia, myelosclerosis and megaloblastic anaemia (Beaven, Ellis and White 1960) (10).

The synthesis of foetal haemoglobin in these conditions arouse several questions :-

1. Does it occur because there is specific difficulty in making one part of haemoglobin molecule which it can replace or because it is an easier process than the manufacture of adult haemoglobin ?

2. Can the appearance of foetal haemoglobin in the anaemia of later childhood and adult life be explained by reversion to foetal erythropoiesis or haemoglobin F synthesis imposed by some acquired disability in erythropoiesis ?

3. What are the other conditions that lead to reappearance of foetal haemoglobin or that delay the maturation of the switch-over mechanism ?

It was with these questions in mind that the present work was planned with the following objectives :-

1. To study the normal values of foetal haemoglobin among normal Egyptian infants and children at different age periods and to compare them with the values reported for other races by other authors.

2. To find out if the endemic factors which affect the growth physically or mentally may prolong or increase the tendency for foetal erythropoiesis. We were particularly interested to study this problem in relation

to Kwashiorkor and marasmus which are very common nutritional disorders among our poor Egyptian children. Our study included as well cases of congenital heart disease, cyanotic and non cyanotic, cases of cretinism and cases of cerebral palsy; being all examples of conditions associated with physical and/or mental retardation.

REVIEW OF LITERATURE

I. The structure of the haemoglobin molecule :

Haemoglobin is an unusual conjugated protein, both chemically and physiologically. Its primary function is to allow a rapid efficient uptake of oxygen from the lungs at the moderate partial pressure of this gas available in alveoli, and virtually as prompt to release oxygen at the low oxygen tension of tissues. The uptake of oxygen is not oxidation but oxygenation, The iron atom remains ferrous and oxygen retains its distribution as in oxygen gas[16,59,62].

The molecular weight of human haemoglobin is 66,000. Its dimensions are 64 Å , 55 Å , 50 Å . The molecule consists of 2 pairs of folded chains which are tetrahedrally placed in respect of each other. Both pairs of polypeptide chain differ in amino acids composition. The foldings of the pairs of chains are similar but not identical. There are eight right stretches called (A, B, C, D and so on) in which the polypeptide chain is alpha helically wound. Between them are parts that are not helically wound. These are the parts where the polypeptide chain changes its direction [62,18,59].

The haem groups are situated between the loops of polypeptide chain[77,13]. For this reason the 4 iron atoms

of the haem groups are relatively far apart. The haem group is attached by covalent bond to a histidine group of polypeptide chain. The forces that keep the four chains together are relatively weak. The 2 pairs of chains in adult haemoglobin are called arbitrarily alpha and beta chains (57,87). The amino acid composition of both alpha and beta chains show the same pattern. There are however, differences, the alpha chain is somewhat shorter than the beta chain (141 to 146 amino acids). At 61 places there is an agreement in amino acid sequences of alpha and beta chains (80,89,112).

II. Structure of foetal haemoglobin :

Foetal haemoglobin is the main component in the blood of newborn. It contains a normal alpha chain and a non alpha chain which resembles the beta chain, counting the same number of amino acids, but differing from it by replacement of 39 amino acids by others. It is called a gamma chain. It contains 4 isoleucine residues which are not found in either alpha or the beta chain. Three proline residues present in beta chain have been replaced by other amino acids (see figure 1) (80,89,112).

Table I

Amino Acid Sequence of the Alpha Chain (80)

Val - Leu - Ser - Pro - Ala - Asp - Lys - Thr - Asp

Val - Lys - Ala - Ala - Try - Gly - Lys - Val - Gly

Ala - His - Ala - Gly - Glu - Tyr - Gly - Ala - Glu

Ala - Leu - Glu - Arg - Met - Phe - Leu - Ser - Phe

Pro - Thr - Thr - Lys - Thr - Tyr - Phe - Pro - His

Phe - Asp - Leu - Ser - His - Gly - Ser - Ala - Glu

Val - Lys - Gly - His - Gly - Lys - Lys - Val - Ala

Asp - Ala - Leu - Thr - Asn - Ala - Val - Ala - His

Val - Asp - Asp - Met - Pro - Asn - Ala - Leu - Ser

Ala - Leu - Ser - Asp - Leu - His - Ala - His - Lys

Leu - Arg - Val - Asp - Pro - Val - Asp - Phe - Lys

Leu - Leu - Ser - His - Cys - Leu - Leu - Val - Thr

Leu - Ala - Ala - His - Leu - Pro - Ala - Glu - Phe

Thr - Pro - Ala - Val - His - Ala - Ser - Leu - Asp

Lys - Phe - Leu - Ala - Ser - Val - Ser - Thr - Val

Leu - Thr - Ser - Lys - Tyr - Arg

Table II

Amino Acid Sequence of Beta Chain [80]

Val - His - Leu - Thr - Pro - Glu - Glu - Lys - Ser
Ala - Val - Thr - Ala - Leu - Tyr - Gly - Lys - Val
Asn - Val - Asp - Glu - Val - Gly - Gly - Glu - Ala
Leu - Gly - Arg - Leu - Leu - Val - Val - Thr - Pro
Try - Thr - Glu - Arg - Phe - Phe - Glu - Ser - Phe
Gly - Asp - Leu - Ser - Tnr - Pro - Asp - Ala - Val
Met - Gly - Asn - Pro - Lys - Val - Lys - Ala - His
Gly - Lys - Lys - Val - Leu - Gly - Ala - Phe - Ser
Asp - Gly - Leu - Ala - His - Leu - Asp - Asp - Leu
Lys - Gly - Thr - Phe - Ala - Thr - Leu - Ser - Glu
Leu - His - Cys - Asp - Lys - Leu - His - Val - Asp
Pro - Glu - Asn - Phe - Arg - Leu - Leu - Gly - Asn
Val - Leu - Val - Cys - Val - Leu - Ala - His - His
Phe - Gly - Lys - Glu - Phe - Thr - Pro - Pro - Val
Glu - Ala - Ala - Tyr - Glu - Lys - Val - Val - Ala
Gly - Val - Ala - Asp - Ala - Leu - Ala - His - Lys
Tyr - His

Table III

Amino Acid Sequence of the Gamma Chain (80)

Gly - His - Phe - Thr - Glu - Glu - Asp - Lys - Ala

Thr - Tie - Thr - Ser - Leu - Tyr - Gly - Lys - Val

Asn - Val - Glu - Asp - Ala - Gly - Gly - Glu - Thr

Leu - Gly - Arg - Leu - Leu - Val - Val - Tyr - Pro

Tyr - Thr - Glu - Arg - Phe - Phe - Asp - Ser - Phe

Gly - Asp - Leu - Ser - Ser - Ala - Ser - Ala - Tie

Met - Gly - Asn - Pro - Lys - Val - Lys - Ala - His

Gly - Lys - Lys - Val - Leu - Thr - Ser - Leu - Gly

Asp - Ala - Tie - Lys - His - Leu - Asp - Asp - Leu

Lys - Gly - Thr - Phe - Ala - Glu - Leu - Ser - Glu

Leu - His - Cys - Asp - Lys - Leu - His - Val - Asp

Pro - Glu - Asn - Phe - Lys - Leu - Leu - Gly - Asn

Val - Leu - Val - Thr - Val - Leu - Ala - Tie - His

Phe - Gly - Lys - Glu - Phe - Thr - Pro - Glu - Val

Gln - Ala - Ser - Tyr - Gln - Lys - Met - Val - Thr

Gly - Val - Ala - Ser - Ala - Leu - Ser - Ser - Arg

Tyr - His

III. Haemoglobin synthesis :

Haemoglobin synthesis starts early during the differentiation of the erythrocyte in the bone marrow and other erythropoietic sites. It starts at the pro-erythroblastic stage and may go on even after the riping red cell has lost its nucleus and has become a reticulocyte already circulating in the peripheral blood (91,8). Incorporation studies with C^{14} labelled amino acids have shown that not all reticulocytes are able to synthesize haemoglobin. The percentage of reticulocyte that are synthesizing haemoglobin in the foetus is higher than in the infant. The synthesis of the polypeptide chain of globin takes place along the surface of specific messenger riboneucleic acid (RNA) molecule which is in contact with 4 or 5 ribosomes. The combination of the messenger RNA with the ribosomes forms one functional synthesizing unit, an ergosome (18,96,113).

The messenger RNA provides the formation for the amino acid sequence in the polypeptide chain of the globin which is synthesized. Before incorporation in the polypeptide chain the amino acids have to be activated by specific transfer RNA. A special enzyme regulates the reaction of transfer RNA with different amino acids.

The synthesis of polypeptide chain on ribosomal aggregate start with the N terminal residue and ends with the C terminal one (123,89).

The messenger RNA molecule that forms the essential part of these ribosomal aggregates is replaced by a new one which has been formed in red cell nucleus after a certain number of polypeptide chains has been synthesized. The frequency of the replacement is unknown. In reticulocytes this replacement is no longer possible, and this may be the reason why haemoglobin synthesis may soon come to standstill (16,93,34).

After the polypeptide chain has been synthesized, it coils together with its normal tetrahedral structure. Before or during this process the haem group must get attached to it. Four polypeptide chains together with four haem groups form one haemoglobin molecule. When not enough haem groups are synthesized e.g. owing to a lack of iron, the synthesis of the polypeptide chains comes to standstill. Globin chains without attached haem have not been found in the erythrocyte (18,119).

IV. Evolution of haemoglobin :

Pauling, Itano and Ingram (86) have put forward the theory that during evolution a primitive haemoglobin