AIN SHAMS UNIVERSITY

FACULTY OF MEDICINE

Department of Pediatrics

THYROID FUNCTIONS IN BETA - THALASSEMIA MAJOR IN EGYPTIAN CHILDREN

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BY

KHALID SAID MAHFOUZ

M. B. B. ch.

UNDER THE SUPERVISION OF FROM THE PEDIATRIC DEPARTMENT

SAADIA ABD EL FATTAH

PROFESSOR OF PEDIATRICS AIN SHAMS UNIVERSITY

SAWSAN EL SOKKARY

ASSIST. PROF. OF PEDIATRICS AIN SHAMS UNIVERSITY

FROM THE ENDOCRINOLOGY DEPARTMENT

HUSSEIN EL DAMMASY

ASSIST. PROF. OF MEDICINE AIN SHAMS UNIVERSITY

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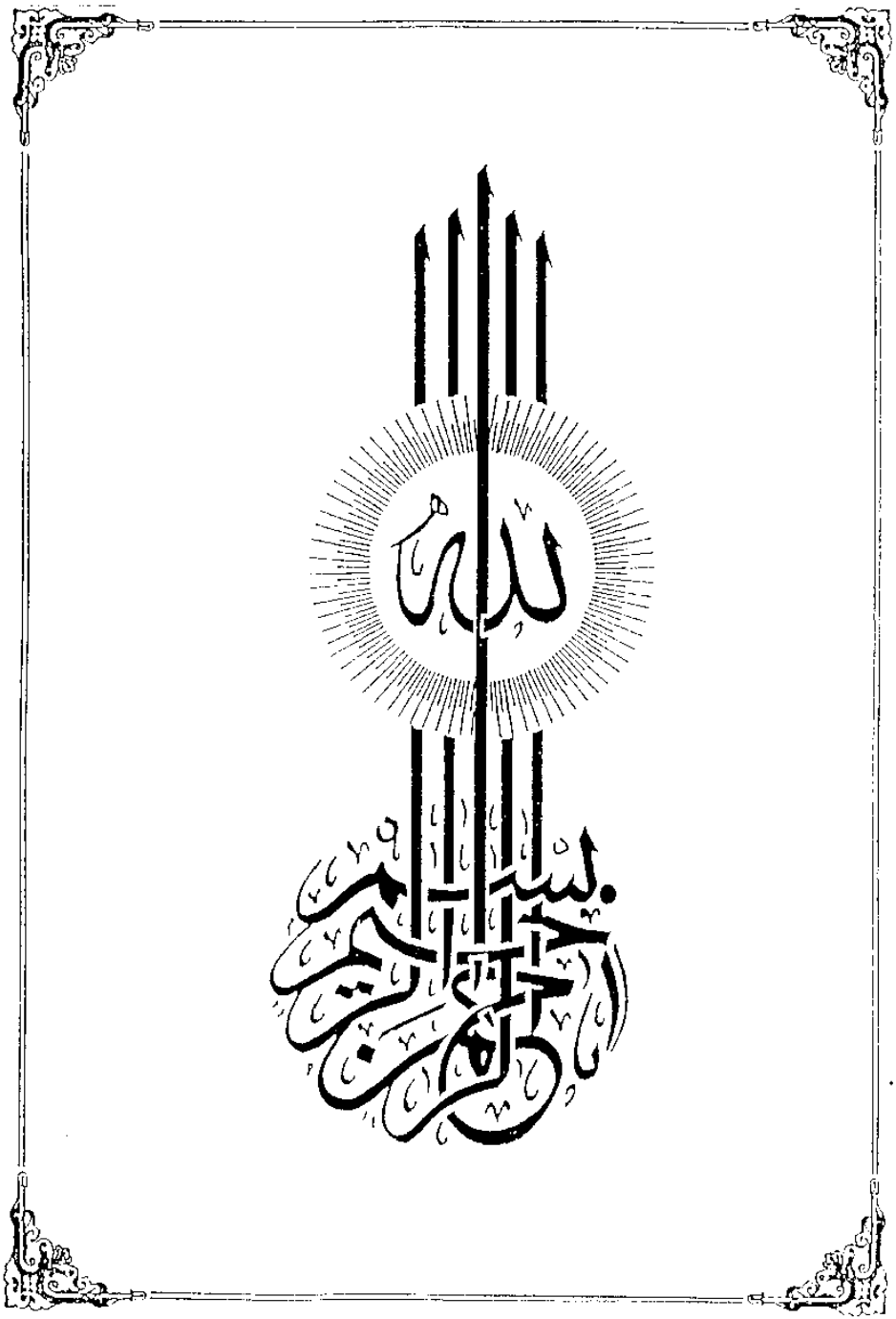

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INTRODUCTION

The thalassemia syndromes are inherited disorders of hemoglobin synthesis characterized by defects in the rate of production of one or more of the globin protein chains associated with ineffective erythropoiesis.

The B thalassemias are a heterogeneous group of disorders charaterized by a decreased synthesis of B globin chains (B^+) or by a complete absence of B globin chains (B^o). They can be divided further into the heterozygous state (thalassemis minor) and homozygous state (thalassemis Major and thalassemis intermedia) the most common variety of thalassemias is B-thalassemia Major (Pepe et al., 1980).

The gene is prevalent in the areas around the Mediterranian sea, and it is the most common hemolytic anemia in Egypt,(Sabri, 1973).It is well known that growth is always retarded in chronic hemolytic anemias, amongst which Beta-thalassemia stands. It has been ascribed to the chronic hypoxia associated with anemia.

On the other hand, hormonal insufficiency may be at least a contributary cause suggested by the findings of massive haemosiderosis in endocrine glands at necropsy. Johnston et al.,1966 and Flynn et al., 1976, suggested that the retardation of skeletal maturation in thalassaemic children is due to hormonal disturbances resulting from chronic anemia or chronic deposition of iron on the glands responsible for the growth spurt.

Thyroxine and or Triiodo thyronine are essential for normal growth and development throughout the growing period, as well as their absence causes disorders and prevent normal develpomental changes.

During childhood the diagnosis of a patient suspected of having an endocrine disorder must involve evaluation of the level and pattern of somatic and sexual growth as well as application of tests to measure the specific hormonal functions.

AIM OF THE WORK

Homozygous B thalassemia is known to be associated with frequent endocrinopathies. One of the endocrine glands which is implicated is the thyroid gland.

The present investigation was undertaken to determine the extent to which the thyroid gland is affected functionally in patients with thalassemia major maintained on regular transfusion regimen, compared with the control group of the same age and sex.

Weight and height of these patients will be correlated with the degree of thyroid dysfunction.

REVIEW OF LITERATURES

Normal human hemoglobins

1- Embryonic hemoglobins:

The Gower hemoglobin and Hb portland are detectable only in the first three months of fetal development.

Epsilon and Zeta chains are probably synthesized in the yolk sac (Kamazera,1974).

2- Hemoglobin F: $\alpha_2\gamma_2$

It is the main component during fetal development. The fetal red cells have a considerably higher oxygen affinity than do adult red cells.

The discrepancy in relative oxygen affinities is due to the diminished interaction of HbF with red cell organic phosphates (Bauer et al, 1968). The red cells of the newborn contain about 80% HbF, 20% HbA (α_2 B_2) and less than 0.5% Hb A_2 ($\alpha_2\delta_2$).

Shortly before birth there is a switch from γ chain to B chain synthesis.

Hb F falls steadily following birth, approaching the normal adult value at about age of six months, Fetal hemoglobin presists longer in infants born prematurely (Garby et al, 1962).

There is a more rapid decline of Hb F in neonates having increased red cell destruction such as in erythroblastosis fetalis.

Hb F is increased to a variable extent in several hereditary disorders, including beta thalassemia, hereditary presistence of fetal hemoglobin and sickle cell anemia.

In addition, increased levels of Hb F may be seen in a variety of acquired hematologic disorders including megalobastic anemia, aplastic anemia and Leukemias (Josephson et al., 1958).

3- Hemoglobin A: ($\alpha_2 B_2$)

In adult red cells HbA makes up over 90% of the total hemoglobin.

4- Hemoglobin A_2 : ($\alpha_2 \delta_2$)

This minor component is distributed among red cells (Heller and Yakulis, 1969) its functional behaviour is probably the same as that of HbA (Bunn and Briechl, 1970).

The percentage of HbA, may be increased in megalobastic anemia (Josephson et al., 1958) in contrast, Hb A_2 is decreased in iron deficiency (Chernoff, 1964) and sideroblastic anemias (Reed and Mollin,1968 and White et al., 1971).

THE THALASSEMIAS

Thalassemia syndromes are a group of hereditary disorders in which there is a defect in the synthesis of one or more of the normal polypeptide chains of hemoglobin.

Cooley's anemia is characterized by decreased synthesis of B globin chains.

Prevalence:

Since the first description of Mediterranean anemia by Cooley & Lee in 1925 the disease has been reported in many races and is no longer thought to be confined to people from the area bordering the Mediterranean sea (Nasab, 1978).

Sabri, 1973 denotes that B. thalassemia Major is the most common hemolytic anemia in Egypt. Allison, 1954, denotes that the gene is present in Africa, Southern Europe and Asia.

It is believed that selective increase in the gene in this area (which may reach an incidence up to 50% in isolated communities) is due to the fact that the heterozygote has an increased resistance to malaria. It is believed that malaria has exerted a selective pressure for the propagation of the thalassemia genes (Weatherall and Clegg, 1972). Although the scientific basis for the protection of the thalassemia (heterozygote) against malaria is unknown.

The B-thalassemia major is also prevalent in the far east (Chernoff et al, 1956) & occurs with considerable freaqency among African (Oleson et al., 1959, Charache et al., 1976).

In Southern Italian and Greek populations about 10% of individuals are heterozygous for B thalassemia. In Thailand as many as 20% of the population carry the trait for one or another type of thalassemia (Wasi et al., 1969). It is now clear that thalassemia has a world wide distribution (Chernoff, 1959; Weatherall & Clegg,1972).

Prognosis :

Although the prognosis has improved significantly, very few patients survive into adult life, the majority reach adolescence.
The decreased life expectancy is largely due to the long term hazard of iron overload as well as increased liability to infection, episodes of severe anemia may be precipitated by infection or folic acid depletion.

The prognostic improvement is due to the use of antibiotics and chelating agents to remove iron and prevent hemo siderosis.

Spotlights on B. thalassemia major as a genetic disorder

- Cooley's Anemia is a recessively inherited disease (autosomal).
- In Mediterranean or cooley's anemis, Hb A ($\alpha_2 B_2$) is reduced or absent and Hb F ($\alpha_2 \gamma_2$) and Hb A_2 ($\alpha_2 \delta_2$) are relatively increased.
- Consanguanity has an important role in its prevelence.
- There is a demonstrable accumulation of excess free α chains within cells as a result of the unbalanced production in which the rate of α chain synthesis exceeds that of β and δ chain synthesis. Such free α chains are unstable and repidly precipitated within the cell. They are the source of the large insoluble inclusion bodies present in the majority of marrow normoblasts.
- The more severe type sometimes designated B^o gene results in zero synthesis of B chain in the homozygous state, only Hb F & Hb A_2 being synthesised; the other type results in only partial suppression of B chain (B^+ thalassemia).
- Tables 1 & 2 shows Heterozygous and homozygous state of B thalassemia (Lanskowsky, 1980).

Table 1. Heterozygous state of B-thalassemia and variants

Type	Hb A_2	Hb F
B^+ thalassemia	increased	Normal
B^o "	"	"
$\delta\beta$ thalassemia	Normal	Increased (2-10%)
H.P.F.H	"	" (10-40%)

Table 2. Homozygous state of B-thalassemia and variants

Type	Anemia	δ globin	B. globin synthesis	B. globin M.RNA	B. globin genes
B^+ thalass	Severe	Present	decreased	decreased	present
B^0 "	"	"	absent	absent	"
δB "	Mild	absent	absent	absent	Deleted
HPFH		"	"	"	"

Likewise B chains are produced two or three times faster than α chains in the usual form of α-thalassemia [HbH disease (B_4)].

In the most severe, homozgous form of α-thalassemia [Hb Bart's (γ_4) hydrops fetalis syndrome] there is total absence of any α-chain synthesis.

Two other disorders, δB thalassemia and HpFH (hereditary pre-sistence of fetal hemoglobin) are related to thalassemia.

The so called Keihauer-Betke technique is useful in distinguishing thalassemia and HpFH (Lewis, 1980). The Fundamental biochemical defect is thought to be quantitative reduction in the amount of messenger RNA (m RNA) for the affected chain (Nathan et al., 1971). This may imply that thalassemia is in fact a "Controller" gene disease.

PATHOPHYSIOLOGY OF THE ANEMIA IN THE THALASSEMIC PATIENTS

The decrease in the synthesis of globin chains of Hb A will result in a decrease in Hb A synthesis and cause a hypochromic, microcytic anemia with low MCH (Mean corpuscular hemoglobin) level of the red cells.

This is applied in both homozygous and heterozygous states.

In Homozygous state, another process worsens the anemia and is responsible for the major clinical manifestations of thalassemia. The continued synthesis in normal amounts of the unaffected globin chain results in the accumulation of excessive amounts of these normal chains within the red cells. These chains form aggregates, precipitate within the cell, and become attached to the cell membrane (weatherall et al., 1969) these precipatates lead to membrane damage. (Gunn et al., 1972) and premature destruction of the red cell (Nathan and Gunn., 1966, Nathan et al., 1969).

In B- thalassemia the resulting α chain aggregates are called inclusion bodies which differs from the total precipitated Hb (α_2 B_2) in the form of true Heinz bodies

Those cells which have the most HbF are those which will have the least relative excess of α chains, since γ chains combine with α chains to form HbF.

It has been demostrated in B-thalassemia that Hb A has a more rapid turnover (Shorter life span) than Hb F (Gabuzda et al., 1963).

Those containing mainly Hb A are short lived and those containing much more Hb F have longer survival (Gabuzda et al., 1963).

The centrifugation of red cells in B- thalassemia reveals that the older, more rapidly sedimenting red cells contain much Hb F and have few α chain inclusions, whereas the younger, more slowly sedimenting cells, are relatively deficient in Hb F and contain many α chain inclusions (Loukopoulos and Fessas 1965, Nathan and Gunn 1966, Nathan et al., 1969).

There is also positive correlation between the severity of the disease in B- thalassemia, the size of the α chain pool and the degree of α to non α globin chain imbalance. (weatherall et al., 1969.

These findings serve to give a relationship of the α chain inclusions to the hemolytic process and the beneficial role of γ chain synthesis in lessening the imbalance of globin chain synthesis, decreasing the formation of α chain inclusions and thus increasing the red cells survival.

In B- thalassemia, the α chain inclusions are found in large quantities in the bone marrow erythroid precurosors.(Fessas.,1963) and are probably the cause of the marked ineffective erythropoiesis or intra-medullary destruction of erythroid cells which is observed in homozygous B- thalassemia (Finch et al., 1970).

These inclusion bodies are practically never seen in peripheral red blood cells before splenectomy but following splenectomy they appear in large numbers (Fessas., 1963).

Excess iron stores accumulate because of repeated blood trans fusions and increased gastro-intestinal absorption (Erlandson et al., 1962; Bannerman et al., 1964; Necheles et al., 1969 &Heinrich et al., 1973).

This iron cannot be utilized owing to the decreased globin synthesis.