GLYCOSYLATED HAEMOGLOBIN (HbA1c)

IN

B-THALASSAEMIA MAJOR .

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A thesis submitted for partial fulfilment

of the requirments of M.Sc pediatrics

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Hb-Alc was found to be elevated in patients with diabetes mellitus , and its level is directly proportional to tha degree of hyperglycaemia . (Bunn , 1976) .

Since,the life span of normal red cell is 120 days the glycosylated hamoglobin (Hb-Alc) level is a reflection of average hyperglycaemia over the preceeding four months . (Gabby , et al , 1977) .

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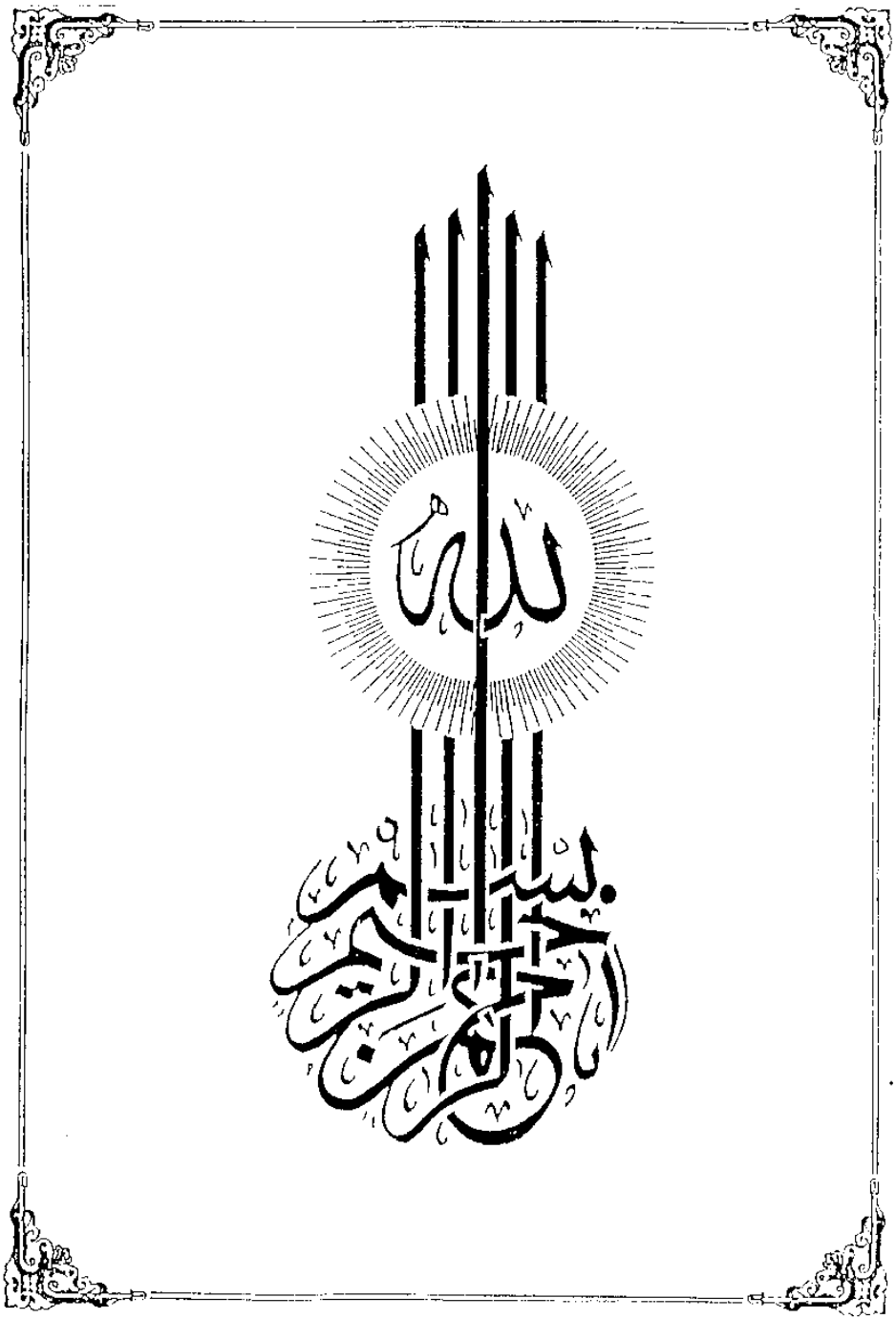

Aim of the work :-

The aim of the present study is to investigate the level of glycosylated haemoglobin (Hb-Alc) in patients with B - thalassaemia major receiving hypertransfusion regimen. An attempt to correlate the level of Hb- Alc with that of blood sugar ; fasting and two hours post prandial , is also considered .

REVIEW OF LITERATURE

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THALASSAEMIAS

B-thalassaemia major is the commonest chronic haemolytic anaemia in Egypt. (Sabry,1973)

DEFINITION:

Haemoglobin is tetramer consisting of two different pairs of polypeptide chains;each with a haem group bound covalently at a specific site, In human, there are at least six different globin polypeptide chains,alpha α ,beta β ,gamma γ delta δ ,epsilon ε ,and zeta ζ.

In normal individuals,synthesis of the α and non α globin chains of the haemoglobin molecule is balanced,producing $\alpha_2\gamma_2$ (fetal haemoglobin)or $\alpha_2\beta_2$(adult haemoglobin),Such balanced synthesis is important if the red cells are to be normal in size,shape and survival.

Thalassaemias are named after the specific globin,whose synthesis is depressed. Most cases are of the α or β type, less common is $\delta\beta$-thalassaemia in which two globin genes are affected simultanously, γ and δ thalassaemia are very rare. Occasionl form of thalassaemias are associated with

the production of an abnormal haemoglobin in addition to the reduced synthesis of normal globin ..Most important of these, is the haemoglobin lepore syndrome:which is related to the B-thalassaemia. Once it had become apparent,that thalassaemia was an inherited condition,it was realized that the parents of the children with severedisorder often show minor haematological abnormalities, including slight anaemia , thus the terms major and minor were introduced.

As it became possible to study globin chain synthesis rates, reduced synthesis of specific globin chain could be pinpointed as the hall mark of thalassaemia,and the specificities "α" and "B" could be added to the thalassaemia nomenclature. Then,with further insight,into the genetic basis of these conditions,the term heterozygous thalassaemia or thalassaemia triat was introduced as an alternative to the clinical lable of thalassaemia minor. It was not unnatural that the term homozygous "B " thalassaemia should then be applied to the thalassaemia major condition of children, both of whose parents had the minor condition and presumbly carried a B-thalassaemia gene.However,recent work at the DNA level indicates that there are a number of B-thalassaemia alleles(alternative gene forms).Thus,a patient with B-thala-

ssaemia major may have two differents,but defective alleles, in such cases the term"homozygous" would be incorrect.

Probably, the phenotypic lable of B-thalassaemia major should be retained until the genetic basis have been fully worked out. (Kandell :1983).

A further complication is caused by the fact that some B-thalassaemia genes are associated with a total failure of B- chain synthesis (B^{0}-thalassaemia), while others lead to a reduced globin production (B^{+}-thalassaemia). In the simple heterozygote the two conditions are clinically indistinguishble but in the homozygous condition total absence of Hb-A indicates B^{0}-thalassaemia (in which B messenger RNA is either absent or present in a non functioning form),while B^{+}thalassaemia is suggested by reduction of B-chain synthesis to 5-30% of normal.(Weatherall,and Clegg,1981).

In terms of clinical significance the distinction is of little importance , What merits comment is that the two conditions have different genetic mechanisms .The first thalassaemia syndrometo be recognized was the severe form of B-thalassaemia ,α-thalassaemia was not recognized until later, because there is no syndrome equivalent to B-thalassaemia major . Recognition came when the technique for globin

chain synthesis analysis and for electronic counter determination of red cell indices revealed that reduced B-globin synthesis was very common in certain populations.

Terminology for the α-thalassaemia syndrome has no relationship to genetic mechanism. (Kandell, 1983).

CLINICL PICTURE OF B-THALASSAEMIA :

Homozygous thalassaemic patients usually become symptomatic as a severe progressive haemolytic anaemia during the second 6 months of life . Regularly spaced blood transfusion necessary to prevent profound weakness and cardiac decompensation due to anaemia .

In response to severe anaemia and haemolysis,hypertrophy of erythropoietic tissues occurs in medullary locations.

Spleen and liver are enlarged because of extramedullary haematopoiesis and haemosiderosis.

In older patients,the spleen may reach such size that causes mechanical discomfort and secondery hypersplenism, Cardiac complications,such as pericarditis and chronic heart failure are frequent terminal events,. Death usually occurs during second decade. (Weatheral&Nelson ,1981).

However,the height failure is more than that of the weight, this could be explained by the excess weight added by the enlarged viscera particularly the spleen .(Khalifa, et al, 1981).

The growth is impaired due to the low level of growth hormone. (Khattab ,et al ,1981). Recently, Mokhtar, et al ,(1983) reported that the growth pattern revealed marked retardation both in height and weight..

DIAGNOSIS OF B-THALASSAEMIA :

The definitive diagnosis depends on the demonestration of unbalanced globin chain synthesis , this is usually studied in reticulocytes,where an α /nonα ratio greater or less than 1.0 implies B orα thalassaemia respectively.

There is a good correlation between the degree of imbalance and severity of clinical syndrome .

The diagnosis of thalassaemia is usually based on indirect laboratory evidenceobtained from simple routine tests . Family studies can sometimes be useful aid to diagnosis .

Most thalassaemia syndromes can be diagnosed with reasonable confidence by the following tests:

- Haemogram .
- Blood film .
- Hb-A_2 level and Hb-F level by haemoglobin electrophresis (on cellulose acetate in alkaline PH).
- Serum iron and percentage transferrin saturation.

B-thalassaemia major is the most clinically significant of the thalassaemias , resulting from the inherit-

ance of two B- thalassaemia genes.

It usually presents during infancy (after normal suppression of Hb-F production has ocurred)as a severe anaemia characterized by microcytosis, target cells,neucleated red cells,and reticulocytosis. In the homozygous B^{O}- thalassaemia there is no Hb-A production, thus only Hb-F and Hb-A2 are found on electrophoresis, In severe B^{+}-thalassaemia major syndrome , some Hb-A is formed (usually <15 % total Hb).Quantification of Hb-$A_2$is of little value . When globin chain synthesis studies are done, they show a marked imbalance .

Precipitation of the excess α chains in the red cells is believed to cause damage to the cell membrane, leading to premature cell destruction, either in bone marrow or the peripheral circulation. Thus the anaemia is the result of defective globin production, ineffective erythropoiesis and increased haemolysis .(Kandell,1983)

PROGNOSIS AND MANAGEMENT :

The prognosis of untreated homozygous thalassaemia is in most cases grave . The infant with thalassaemia major is not born with significant anaemia, although def-

icient B- chain synthesis can be demonestrated at birth. (Gaburro , et al , 1970 ,) .

Symptoms are rarely noted in the firest 6 months of life . Most affected children develop clear evidence of severe anaemia by the end of the second year of life . (Smith, et al , 1978 ,) . In most untreated cases death occurs prior to 5 years of age .

In the past transfusions were given every 5 to 10weeks. They were given only when symptoms of severe anaemia, such as fatigue , weakness, and level was permitted to fall 5.0 to 6.0 gm % or even lower , the children were symptomatic much of the time . Further , because erythropoiesis was not suppressed, hypertrophy of erythroid tissue occurred in medullary and extramedullary sites as a response to the haemolysis and anaemia . Marrow hypertrophy caused severe and progressive skeletal changes , production of osteoporosis and sometimes disfiguration of facial changes . Severe splenomegaly , primarily caused by extramedullary haematopoiesis , freqently necessitated splenectomy in early childhood . (Smith , et al , 1978.)

In an effort to improve growth , lessen hepatospleno-

megaly, eliminationof fracture, decreese skeletal and facial deformities , diminish gastrointestinal iron absorption and decrease cardiac enlargment , some clinics have initiated transfusion programs designed to ameliorate these symptoms and signs . The minimal level varied somewhat; but in general haemoglobin levels were maintained above 9 to 10 gm / dl . These regimens have been designated hypertransfusion . (Miller , et al , 1976,).

Because hypertransfusion programs require an increase of 25 % or more in the amount of blood to be administered it was feared that this would result in accelerated iron overload , more rapid development of complications , and death at an earlier age . These concerns have not been realized , and the life expectancy of children on hypertransfusion programs does not appear to be significantly shortened . (Smith , et al , 1978.) .

More recently , even more vigorous transfusional programs aimed at keeping haemoglobin levels above 12.0gm/dl have been used to totaly suppress erythropoiesis "supertransfusions" . .(Miller , et al , 1976.).

Iron chelation therapy must be in corporated into any intensive transfusion regimens .