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Liver function in Thalassemia Major

Dr. Iman Abdul Wahhab Hasan[1], Dr. Basma Jasim Obaid[2], Dr. Muntaha Mohammed Murad[3]
[1, 2, 3] Paediatric Central Teaching Hospital, Iraq

Abstract
The study of liver function tests in thalassemia major patients was done. The aim of the study to see the extend liver damage in thalassemic patients. Liver function were estimated in group of 50 thalassemic patients and the results were compared with the results obtained in group of age and sex matched control with normal Hb (HbAA). The liver function were elevated in 32 Thalassemic patients and the remain 18 patients were within normal range, E.I. 64% of the patients got SGOT and SGPT elevation from both sexes. The Alkaline phosphatase was elevated in 52% of cases and there was P.T. time prolongation in 16% of cases. Liver functions were considerably higher in thalassemic patients and the different in their mean compared to the mean in the normal group (HAA) was statistically significant ($P<0.05$), It is suggested that further studies are necessary on liver functions tests on Iraqi Thalassemic patients particularly on older age to assess the extent of liver damage in the Thalassemic patients. Liver functions were elevated mostly in Thalassemic patients after the age of 6 years 68.5% while 31.5% before that age. SCOT and SGPT were mainly elevated with the same value in both sexes. While S-Alkaline phosphatase and pT were elevated in Males > Females. Liver functions were elevated after splenectomy in 64% of thalassemic patient with splenectomy. 86% of the Thalassemic patients included in the study were relatives while 14% were unrelated (Father &. Mother). Liver size is increased in 96% of the cases. 100% of patients got pallor with Hb ranges 5-10g/dL. Linear growth was affected and was more influenced children after the age of 8 years. The age of the Thalassemic patient in the study ranges between 1.3 year > 16 years.

Keywords: thalassemia, patient, children

Introduction
Thalassemia is diverse, heterogeneous group of inherited disorders characterized by defect in synthesis of one or more of the subunit of Hb and in contrast to the qualitative abnormalities. Thalassemia are quantitative abnormalities, of the synthesis thus the B chain of patient with thalassemia are normal in structure but in reduced & some time undetectable amount [8]. This inherited disease (thalassemia) also reduces or totally destroys the body ability to produce healthy hemoglobin. It exist in many form the most sever is (&. thalassemia in which the fetus cannot survive sometime or the other is B. thalassemia major which is characterized by in complete or complete absence of chain synthesis [2]. The pathophysiology of this disorder appear at least in part related to interference with formation of normal adult Hb and shorten survival of the erythrocyte is characteristic [4]. Genetics; thalassemia is genetically determined disease occurs mainly in the Mediterranean area in Asia, It result from imbalanced production of the globin chain which result in defective Hb molecule production so thalassemia differ from other haemoglobinopathies is that Hb molecule synthesized normally but in reduced manner if the defect in &-chain it is called & thalassemia or the defective rate of synthesis involve B chain is called B-thalassemia. Thalassemia is a disease which can be grouped neither with pure recessive or dominant disease and it is said to have an intermediate mode of inheritance as it affect both heterozygote as well as homozygote. The gene of B-chain is normally situated on the chromosome 11 while the gene of &-chain is carried on chromosome 16 [10]. Molecular Pathogenesis of B-Thalassemia is more complex and Heterogeneous, than &-thalassemia. In contrast to &-thalassemia, gene deletion is UN common cause of B-thalassemia. Among the recognized cause of B- gene deletion an entity known as (Hereditary persistence of fetal Hb) has minimal clinical manifestation owing to efficient synthesis of V-chain on the chromosome in which B and £ gene are deleted. In the great majority of cases of B-Thalassemia. Restriction endonuclease maps reveal no gross abnormalities of the B-globin gene complex nevertheless there are several steps in B-globin synthesis that could go awry and lead to thalassemia phenotype. A number of cases involve mutation in or near one of the intervening sequences of the B-globin gene leading to errors in the splicing mRNA often B+ chain are made but in reduced amount (B+ thalassemia as in fig.(l). Other cases have non-sense mutation in the coding region causing premature termination of B-globin chain this is the most common of B° thalassemia. B. Thalassemia: The heterogeneous group of this inherited disorders are characterized by hypochromic anemia caused by defect synthesis of one or more of polypeptide chains of human hemoglobin and because it involve different polypeptide chains, there are variety of thalassemia each of which has characteristic clinical and biochemical manifestation [18]. In the homozygous state B-thalassemia genes result in sever or total suppression of B-synthesis and clinically characterized as thalassemia major or Cooley Anemia. As a consequence of diminished HbA synthesis the circulating RBCs are small, thin, distorted, contain markedly reduced amount of Hb therefore the hypochromic anemia of thalassemia major is so severe that dependency on blood transfusion is usually established at an

early age [9]. In B-Thalassemia as a result of profound decrease in B-chain, there will be reduction or total absence of synthesis of HbA (&2, B2) [2]. As a compensatory response V-chain synthesis is partially reactivated and HbF will increase, also there will be an increase in free &-chain within the nucleated RBCs and Reticulocyte, they aggregate forming unstable unit (Heinz bodies) that precipitated causing the membrane change within the RBGs and their destruction within the bone marrow so erythropoiesis is largely in effective. The few red cells that gain entrance to circulation are small, distorted and burdened with (& globin inclusions and contain markedly decreased complement of hemoglobin (the classical hypochromic microcytic, poikilocytes blood smear of Cooley anemia) [12, 8].

History

During 1925 and 1927 Cooley found a group of children with similar clinical and Hematological abnormalities. The affected children of Mediterranean area. Severely anemic, striking skeletal changes, facial abnormalities and splenomegaly. Their blood contains large numbers of nucleated RBCs leading to Erythroblast called it Cooley anemia.

Geographical distribution

Thalassemia genes occurs commonly in countries boarding on the Mediterranean area (sea). Italy 5%, Greece 5.15%, American Italian 2.5%, turkey, Iran, India, Thailand, Cambodia Black American 0.5-1%.

Pathogenesis

The introduction of DNA technique has permitted an isolation and analysis of normal and thalassemia genes. The homozygous B° Thalassemia beta globin chain synthesis is absent in (1/3) of cases in heterozygous B4 (2/3) of cases. The other factors required for B-chain synthesis normal. The whole complex reaction now mRNA.

Pathophysiology

The anemia of B-Thalassemia major result from intramedullary red cells destructions, shorten RBCs life span and peripheral hemodilution due to increase in plasma volume. It is currently believed that the principal lesion lead to intramedullary cell death and reduce the life span is formation of intracellular aggregate of&-chains. Studies of Hb synthesis have indicated that the deficiency of B-chain production lead to large excess of &-chain within the developing RBCs. In some cells V-chain are able to remove the excess of &-chain as HbF but when chain production is insufficient. The excess of & chain rapidly precipitate and depending on amount of perception. The most severely affected cells are destroyed. Immediately in narrow and the less affected are released to circulations all this lead to infection erythropoiesis. The cx-chain aggregate which appear in circulating cells as methyl violet-positive inclusion bodies interfere with normal RBC membrane function and contribute to reduced survival through this mechanism many cells are damaged or destroyed in circulation or phagocytosed by R.E system in liver and spleen.

Clinical Picture

This condition is characterized by chronic haemolytic-anemia which become manifest later in infancy but not in newborn, pallor is constant, icterus not uncommon. Splenomegaly increases throughout childhood, hepato-megaly, due to extramedullary. Erythropoiesis retardation of growth and development in early childhood, skeletal changes are constant [2 3, 10, 5]. Bone pain, short stature, menarche is often delayed and secondary sexual character are underdeveloped. Epistaxis, skin pigmentation could occur. Sever infection particularly if the spleen is removed. Septicemia is early cause of death. Pericarditis occurs in about half of the patients. Hypersplenism have complex rule in an etiology of anemia often cause come reduction of platelets count. Cardiomegaly and left ventricle deterioration progress to C.C. failure. Arrhythmias may lead to sudden deaths. Kidney often enlarged with dark color urine due to excretion of dipyrone. Adolescent growth spurt delay [9]. Multiple endocrine abnormalities such as hypoparathyroidism pituitary and gonadal dysfunction. The hand may become broaden and thickened due to changes in metacarpal and phalanges. Faces has mongoloid appearance due to thickening of facial bone [1].

Laboratory Investigations

The anemia of Thalassemia major is characterized by sever hypochromic. Microcytic: The child not anemia at birth but first months of life. The Hb level decrease progressively. Hb level could ready 3-5 g/dl without transfusion. The RBCs morphology is strikingly abnormal with microcytes, bizarre, poikilocytes, target cells and leptocytes (large, extraordinary thin, wrinkled and folded cells containing irregular clumps of hemoglobin. Some cells are macrocytes occasional spherocytes, Tear-drop cells are often seen but decrease after splenectomy. The HCV, MCH are significantly reduced while MCHC also reduced. Normoblast could be present especially after splenectomy. Reticulocytes could be raised to 10% specially after splenectomy. WBCs raised with value 15-40 x 109 /l. Platelet count usually normal and could reduce with large spleen [12, 17]. The osmotic fragility is strikingly abnormal decrease (RBC, resist the hemolysis by hypotonic chloride solution). RBCs survival decrease with Cr [21] t (l/2) ranging from 6.5-19 days compared with normal 25-35 days, the indirect Bilirubin is increased S. iron is increased, iron binding protein is fully saturated. Serum and RBCs folate decrease. SGOT, SGPT are increased reflecting hepatic damage, by hemosiderosis* [9, 28] The Hb electrophoresis depends on clinical type. HbF constitutes more than 90% of total. The percentage of HbF bears no relation to the degree of anemia. HbA2 variable and parallel the level of HbA1 with ratio 1:30 normally and increase to less than 1:20. Bone marrow shows intensely Hyperplastic erythropoiesis with increase iron deposition [12, 19].

Complication of B. Thalassemia major

1. Skeletal changes: skeletal abnormalities result from hypertrophy and expansion of the erythroid marrow this result in widening of the marrow space and thinning of cortex with consequent osteoporosis in the skull lead to frontal bossing, prominent malar eminence, depression of the bridge of nose, oblique appearance of eye protrusion of the lip upward exposing upper teeth and by x-ray (hair on end appearance) bony changes lead to Cooley's faces. The earliest selected changes are observed in metacarpal, metatarsal bones.
2. Growth retardation: This probably was a consequence of anemia, tissue hypoxia, iron overload with frequent

blood transfusion when its deposition in tissues resulting in Multiple organic failure like hypothyroidism Hypoparathyroidism, Heart failure, liver dysfunction and cirrhosis. Menarche delayed, breast developed poor, amenorrhea could occur-so small dose of estrogen and progesterone is used to induce cyclic bleeding may be of psychological benefit. Pregnancy reported in patient with thalassemia intermedia only. Boys are frequent immature, spermatogenesis may be normal, libido decrease lack of secondary sexual characteristic could treated with small doses of androgen. Linear growth is the mainly affected.

3. Cardiac abnormalities are frequent and important causes of morbidity and mortality in patient with thalassemia major. The first electro cardio graphical abnormalities to be noted include prolong P.R. interval, first degree heart block and premature atrial contractions. The presence of S.T. depression and supra ventricular ectopic beats constitute omniums indicator of myocardial damage. Pericarditis, sterile attributed to hemosiderosis but an association with B-hemolytic streptococci is suggested. Cardiomegaly and left ventricular deterioration progress to chronic refractory congestive heart failure. Arrhythmia may cause sudden death.
4. The liver and gall bladder. The liver of these patient are much enlarged due to extramedullary hematopoiesis and hepatomegaly can be reduced by hyper transfusions therapy. Later is associated with extensive cirrhosis. Iron deposition at first present at in the Kuepfer cells, ultimately engorge the parenchymal cells resulting in appearance like idiopathic hemochromatosis high incidence of Hepatitis B surface markers (HBs Ag), anti Hbc. and anti Hbs anti-bodies were found. The most important abnormalities of liver function include:
5. Hypergammaglobulinemia, moderate decrease in coagulation factors and increase level of transaminases.
6. Pigmentary gallstones are found in 2/3 of pt. more than 15 years.
7. Multiple endocrine abnormalities.
8. Increase susceptibility to infection especially after splenectomy.
9. Complication of blood transfusion.
10. Neurological complication due to extramedullary hema-topoiesis. Within the spinal cord causing its compress-ions. These neurological complication are rare [15].
11. Complication of iron chelating agent (Deferoxamine) on hearing or vision [20, 16, 9, 2 1, 1 4].

Management of B-Thalassemia Major

The prognosis on B. Thalassemia has improved in recent years and could improve still further if the best available management where to be everywhere pursued, these include: 1-Hypertransfusions scheme in which blood is given regularly to maintain Hb level above 10 gm/dL. So the original aim is to maintain the Hb at the lowest safe level and this usually involve blood transfusion at 5-10 weekly interval. More frequent transfusions were

considered	**unwise**	**because the iron**	**content**	**of**	**The**
transfused	blood	(each unit of blood	contain	200	Mg

Iron). So accelerate development of hemosiderosis and organ failure. The clinical benefits of hypertransfusion therapy was dramatic. Another experimental transfusion program by using young population of red blood cells (neocytes) prepared by cell separators, but these are expensive than ordinary packed RBC. Before transfusion therapy is given (first). Complete genotype of RBC give information for identifying minor blood group in compatibility if iso- immunization should develop later. Blood should be relatively fresh. 2-Chelating therapy with deferoxamine, this should be started when serum ferritin level reach 1000 ug/ml. II used in dose of 50-60 mg/kg/day. S-C. 5 days/wk, the administration of 200 mg of vitamin C orally enhance iron execration. Other chelating agent 2, 3 dihydroxybenzoic acid given orally.

3-Splenectomy: the usual indications for it are: Sheer size (huge) of the organ caused mechanical discomfort., Hypersplenism lead to thrombocytopenia and neutropenia., progressive in shortening of the survival rate of transfused RBCs evidence by increased transfusion requirement (200 ml/kg/year)

1. Bone Marrow Transplantation: This is newly used for the treatment genetic disease such as thalassemia major; the abnormal marrow must be destroyed and replaced by normal marrow. The 1st transplant 1981 more than 500 marrow transplants for thalassemia major have been done. Approximately 10% of the patient died of complications of marrow grafting and 10% have regenerated their own marrow and again have thalassemia major. Eighty percent (80%) of the patients appear to be cured of the disease. Although some 5% of the cared patient are under treatment for chromic GVHD. Good results are new reported for older, multiply transferred patients [8].
2. Gene Therapy: Thalassemia is one of human disease as a candidate for gene replacement therapy. If proper regulation of globin genes could be achieved Thalassemia would constitute an important opportunities because of the accessibility of bone marrows for in vitro treatment [8]. In gene manipulation and replacement also Reactivation -gene function could ameliorate the unbalanced globin chain synthesis resulting in reduction of the Ineffective erythropoiesis and homiletic anemia of the disease. DNA manipulation technique is under trials to make it possible to transfer the correct gene.
3. Abortion is carried out on those fetuses showing either No B-chain production (B°-Thalassemia) or markedly reduced production (B4 thalassemia) after prenatal diagnosis after 20 wks. Gestation [19, 9, 20, 23].

Oral Iron Chelators: Because deferoxamine must be administrated parenterally and because its cost, investigators have searched extensively for an inexpensive orally effective iron chelator. Several initially promising compounds have proven to be toxic in animal studies or ineffective in human trials. Two drugs currently tried in humans and several drugs presently being studied in animal have aroused renewed interest in finding alternative to deferoxamine: Pyridoxine isonicotinoyI hydraxon (PIH) is an expensive oral chelator of two compounds (pyridoxine and isoniazid) that have been used extensively for treatment of other disorders without major toxicity. Total iron excretion in human at doses of PIH tested thus for is less than is obtained with conventional dose of deferoxamine given by subcutaneously infusion. This chelator may be useful for preventing the more slowly progressive iron overload due to in create iron absorption in patients with

thalassemia intermedia and related syndromes. Hydroxypyridine represent another promising class of iron chelators one of these is 1, 2-diamethyl-3-hydroxypyrid 4-one [4]. Induce urinary iron excretion at rate comparable to that obtained by deferoxamine in iron overload patients with thalassemia. This drugs has few side effects when used in human and animal studies [5].

Prenatal Diagnosis and Genetic Counseling

This can be achieved by: 1-Fetal blood sampling at 16-22 wks. Gestation with direct measurement of globin in differentiating affected from non-affected fetuses with homozygous B-Thalassemia. 2-Linkage analysis using multiple polymorphic restriction endonuclease sites. 3-Biopsy of fetal trophoblastic tissue may permit obtaining sufficient DNA from pregnancies as early as 12wks [10, 9, 1, 17].

Patients and Method

Fifty patients aged (15months 8years) where included in this study in AL –KARAMA Hospital in Baghdad during the period between December 2014-1st July 2015 and the following considered

History, physical examination, investigation

By history: Age of patients, Sex, residence, Age of diagnosis, Frequency of blood transfusion, Using of chelating agents regular or irregular Fathers and mothers relative or not. Anemia, Spleen and liver size, liver span, Height. Splenectomized or not? Then investigations: Hb%, PCV, SCOT, SGPT, S. Alkaline phosphatase, P.T. We concentrated on liver functions and we consider. SGOT up to 45 IUIL Normal, SGPT up to 45 IUIL Normal, S. Alkaline phosphatase up to 13 KAy/l Normal, P.T. P.T. (11-15) up to 15 sec Normal.

Method

Blood sample were collected from 50 thalassemic patients and from 50 normal control of the same age and sex. Their mean age was 8 years with range 1.3-16 years. The plasma is separated from the cells by centrifugations was used for the estimation of SGOT and SGPT on Operator called ASTRA and in Saddam Central Teaching Hospital Lab. and by a Kineti method or procedure the liver function analysis was done. The results were collected and statistical analysis were done for each parameter. The statistical significant of difference between the mean for each parameter in thalassemic patients compared to that in the normal individuals was obtained by student's t-test. A P value < 0.05 was considered significant. Another blood samples were collected in heparinized tubes from the 50 thalassemia patients and the 50 normal controls of the same age and sex. Centrifugation was done for 10 minutes, then 0.2ml of reagent is added to 0.1 ml of the plasma and was read after clot is formed. This will give us P.T. estimation. The control work was 14.5. Analysis of the results was carriedout and the difference with the control groups is statistically studied.

Results

From 50 patients studied for liver function test affected by the disease, we found that there was an increase in SGOT in 32 patients from the total No. 50 which represent (64%).There was also an increase in SGPT in a similar No. of the patients 32(64%).The No. of male patients were 20 of thirty two which equal to (62.5%). While the female No. was (12) which represent (37.5). The ratio of male: female of SGPT also the same 20:12 E.I 62.5% and 37.5% females. The No. of patients who an increase in alkaline phosphatase were 26 male and female which equal to 52% of total No.16 males 61.9% of cases & 10 females 39.1% of cases. While there was an increase in the P.T. in 8 patients 16% five of them were males & three females (62.5% and 37.5% respectively). Figure (4) there was no significant increase of liver function enzymes of two patient taking iron chelating agent (Deferoxamine) included in the study. The higher % of an increase in liver function enzymes were in the ages above 6 years 22 patients E.I 68% of ' the total No. of patients studied while 10 patients (31.3%) were below 6 years old as shown in table (1). There was an increase of liver function SGOT and SGPT in 20 males while female 12 to 20:12 but the male: female ratio is highly significant with P.T. 7:1 as shown in table (2). It has been noticed that ten (10) out of 14 patients with splenectomy have an increase in liver function enzymes 71% of cases as shown in table (3). The level of Hb, PCV in thalassemic patient always less than the mean for matched control while there was an elevation of SGOT, SGPT, Alkaline phosphates and P.T. more than the mean as shown as table (4). We found also that 16 patients were above the 3rd. centile of linear growth 32% while 68% (34 patients) below the 3rd. centile. The liver enzymes increase mainly in those are below the 3rd. centile and to lesser extent in the 1st. group, as shown in Figure (2-A, B).

Discussion

Most of our thalassemic patient have hepatic damage secondary to hemosiderosis which lead to an increased serum SGOT and SGPT [9, 17]. We found that liver function affected all age groups in both males and females but mainly above 6 years depending on amount of blood transfused. The effect of SGOT and SGPT in the males is similar to that in female so the same percentages so 62.5% in the male's patients while 37.5% in the female patients have an increase in SGOT, SGPT. Out of 50 patient included in the study 32 patient liver function were mainly affected and all with irregular. Iron chelating agents. There are two patients with regular intensive chelating therapy their liver enzymes were normal so the treatment with deferoxamine will lead to significant decrease in level of SGOT and SGPT and lead to normal linear growth.([20,18]). (Figure 3). In this study we found that livers of these patient were very enlarged as consequence of extramedullary hematopoiesis which can be reduced by hypertransfusion therapy [9, 21, 13]. Oral iron chelators may be used instead of deferoxamine which must be administer parenterally and because its costs.

Conclusion

1. Liver function affection is common among thalassemic patients.
2. SGOT and SGPT are similarly affected and they increase in both females and males.
3. There is high incidence of hepatic damage detected clinically by hepatomegaly and an increase in the seven level transaminase enzymes by lab. Investigations.
4. There is no regular fallow up of thalassemic patient to assess the abnormality of the liver function and its complications.

5. There is delay in detection of abnormality of liver function.
6. All our patients receive the blood to correct anemia and forgetting its effect on decrease liver size.

Recommendation

1. All thalassemic patient should have an assessment to their liver function.
2. All patients should have periodic physical examination for early detection of liver complication and proper management.
3. Education of the families about the nature of the thalassemia, important of hyper transfusion therapy iron chelating should be taken regularly.
4. Marriage among the relative of thalassemic patient should not be encouraged.

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