ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 11, Issue, 04, pp.2933-2946, April, 2019
DOI: https://doi.org/10.24941/ijcr.35096.04.2019

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

PREVALENCE OF SKELETAL CHANGES IN PATIENTS WITH B THALASSEMIA MAJOR IN MOSUL

***Dr. Adeeba J. Mahmood**

Ibn Al_Atheer Hospital in mosul, Iraq

ARTICLE INFO

Article History:
Received 27th January, 2019
Received in revised form
04th February, 2019
Accepted 27th March, 2019
Published online 29th April, 2019

Key Words:

Thalassemia,
Major, Bone Changes.

ABSTRACT

Background: Thalassemia is a herieditary anemia resulting from defects in hemoglobin production. β-Thalassemia which is caused by a decreas in the production of B-globin chains, affects multiple organs and is associated with considerable morbidity and mortality

Aim:

1.To study the radiographic skeletal changes in transfusion dependent thalassemia patients attending thalassemic center in Ibn_Alather Children Teaching hospital in Mosul and to correlate these changes with age.

2.To asses growth retardation in those patients clinically by using normal growth charts comparing them with our records of weights and heights

Setting: The study was conducted in Ibn Al-Atheer Children hospital, Thalassemia center. Mosul city,Iraq from August2009_Octobar 2010 as prospective study. **Patients and Methods:** Five hundred patients whose age ranged between(6month _32 year) were studied. Two hundered patients were examind by x-ray for forearm, hand, skull X-ray. 300 patients take for them Chest X-ray. **Results:** The age of the studied sample ranged between 6 month _32 years. The peak incidence of the patients in the age group 6 month _10 years (29.4%), male to female ratio 1:1.2. Fifty three percent from urban areas and 47% from rural areas. Seventy seven percent of patients diagnosed during the first year of their lifes. Sixty five percent of patients non compliant on chelating agent (desferroxamin). ninty percent their hemoglobin before transfusion range between 7-9gm|dl, 31% had hand bone changes: thinning of bone cortex, fusi form shape metacarpal and phalangyal bone with osteoporosis and localized lucency. Twenty nine percent had abnormal long bone changes highest percentage in the age group 11-14 years, no any case of desferroxamin – induced bone dysplstic changes,71% of patients had osteoporosis of ribs, no any case of thoracic extramedullary hematopoiesis. Fourty two percent of patients their weights fall below 5th centil and 56% of their height fall below 5th centil **Conclusion:** Radiological skeletal changes in our patients is high in comparison to other thalassemic patients in other studies which is due to poor compliance of these patients to both blood transfusion and chelating agents.

**Corresponding author:*
***Dr. Adeeba J. Mahmood**

***Citation: Dr. Aeeba J. Mahmood,* 2019.** "Prevalence of skeletal changes in patients with B Thalassemia Major in Mosul.", *International Journal of Current Research*, 11, (04), 2933-2946.

INTRODUCTION

Thalassemia is a hereditary anemia resulting from defects in hemoglobin production. β-Thalassemia, which is caused by a decrease in the production of β-globin chains, affects multiple organs and is associated with considerable morbidity and mortality (Deborah Rund, 2005) β-thalassemia is among the most common genetic disorders worldwide. The clinical spectrum of β-thalassemia ranges from the severe transfusion-dependent β-thalassemia major to the a symptomatic β-thalassemia carrier (Alireza Fotouhi Ghiam, 2010). The thalassemia major is the most prevalent type of thalassemia as its homozygous state (Kamal mansi *et al.,* 2009). Homozygous β-thalassemia major is a transfusion –dependent, autosomal recessive haeglobinopathy with highest prevalence in the Mediterranean countries, India. and South –East Asia, worldwide, 60 000 children are born each year with β-thalassemia major (Eva Marie Erfurth *et al.,* 2004). The total annual incidence of symptomatic individuals is estimated at 1in 100,000 throughout the world and 1 in 10,000 people in the European union (Gal Renzo anello, 2010). The severe forms of the disease are especially prevalent in small countries where there are close family marriages (consanguinity) (Anita Catlin, 2003).

Pathophysiology: Two major features contribute to the pathogenesis of sequelae of B-thalassemia : in adequate B-globin gene production, leading to decreased levels of normal hemoglobin (HbA), and an imbalance in alpha and beta globin chain production. In bone marrow, thalassemic mutations

disrupt the maturation of red blood cells, resulting in ineffective erythropoiesis the marrow is hyper active, but the patient has relatively few reticulocytes and severe anemia (Robert M, kligman, 2007). The excess unmatched alpha–globin chains accumulate in the growing erythroid precursors causing their premature death (ineffective erythropoiesis) (Orky Weizen *et al.,* 2006). In bone marrow, the alpha chain inclusions precipitate in the normoblasts, which are destroyed within the bone marrow before reaching reticulocyt stage causing in effective erythro-poiesis. The cells that gain entry in to the circulation are small, distorted and filled with inclusions. They also contain a very small amount of hemoglobin that produces the typical microcytic hypo chromic appearance of RBCs (Baker, 2000). These increased erythropoiesis causes expansion of bone marrow cavities, which may contribute to the reduction of bone mass and increases incidence of fractures. The pathogenesis of bone changes in thalassemia is not yet known. One explanation has been offered that increased erythropoiesis demand more bone marrow space through reduction of trabecular bone tissue. Previous studies have shown multiple factors may act in concert to produce bone disease in thalassemia these include hypogonadism, delayed puberty, iron deposition, vit. D deficiency, and desferioxamin toxicity in bone (Pat Mahachoklertwahana, 2003).

Clinical manifestation of thalassemia major: β-Thalassemia is characterized by chronic hemolytic anemia which becomes manifest later in infancy but not in the newborn. Pallor is constant and icterus not uncommon. Splenomegaly increases throughout childhood. hepatomegaly is also present, largely due to extramedullary erythropoiesis. The facies has a mongoloid appearance due to thickening of the facial bones (Krishna *et al.,* 2009). Growth retardation in patient with thalassemia major is probably multifactorial and may be caused by inadequate transfusion, iron overload with hypothalamic pituitary function derangement and or deferoxamine toxicity. Short stature is primarily due to a decrease in sitting height, which in turn, is related to deferoxamine toxicity on spinal growth. bone age is delayed (Chan, 2002). In adolescence, secondary sex characteris-tics are delayed. The skin color becomes ashen-gray due to the combination of pallor, jaundice, and hemosiderosis. Patient also presents cardiomegaly, hepatomegaly, and splenomegaly. Bimaxillar protrusion and other occlusal abnormalities are frequent abnormalities include spacing of teeth open bite, prominence malor bones, protrusion of maxilla and saddle nose (Salehi, 2007). Although conventional therapy such as repeated blood transfusions as well as iron chelation to reduced iron overload has improved clinical features of the disease, severe complications such as liver and heart disorders, viral infections and dysfunction of the endocrine system remain among the major causes of poor quality of life and high mortality (Feng *et al.,* 2006). Transfusion –transmitted infection (primarily hepatitis B and C) are an important cause of death in countries where proper testing is not available (Deborah Rund, 2005). Endocrine dysfunction may include hypothyrodism, gonadal failure, hypoparathyriodism, and diabetes mellitus. Congestive heart failure, and cardiac arrhythmias are potentially lethal complications of iron storage in individuals with thalassemia (Robert and kligman, 2007). Abnormal hematopoietic tissue usually develops in sites responsible for fetal hemopoiesis, such as spleen, liver, lymph node and kidney; however, other regions such as spine may also become involved and may occasionally lead to progressive spastic myelopathy (Udita Dewan, 2010).

Laboratory study:

Hematological testing: Anemia is usually moderate to severe at time of diagnosis. The white cell count may be falsely elevated due to presence of nucleated red cells. Platelet count is normal. There is marked hypochromia, microcytosis anisocytosis, poikilocytosis, target cells and nucleated red cells. diagnosis is confirmed by hemoglobin electrophoresis which shows increase in fetal Hb (Hb F) (Asha Shah, 2004). The Hb pattern in beta thalassemia varies according to beta-type. In beta-zero thalassemia, homozygous HbA is absent and HbF constitutes the 92-95% of the total Hb. In beta plus thalassemia homozygus HbA levels are between10 and 30% and HbF between 70- 90%. Hb A2 is variable in beta thalassemia homozygous (Gal Renzo anello, 2010). Serum ferritin concentration is a convenient and commonly used marker of total iron concentration. However, it is affected by hemolysis, in effective erythropoiesis, inflammation, and liver disease and its accuracy in the estimation of body iron under these circumstances has been shown to be unreliable (Chan, 2002).

Imaging study: The main pathological change that leads to radiological skeletal changes in beta thalassemia is extensive marrow proliferation. The severity of the skeletal responses is related to the type of thalassemia, the extent and duration of the disease, the type of treatment and the volume of blood transfusions given to the patient as well as the side effects of transfusion –chelation therapy and also depends on the bone involved (Bedir *et al.,* 2008) Osteoporosis represents an important cause of morbidity in adult patients with thalassemia major. The pathogenesis of osteoporosis in thalassemia major is multifactorial, and include bone marrow expansion, endocrine dysfu-nction and iron over load (Ersi Voskaridou, 2004). The Odontofacial manifestations that are diagnostic of thalassemia and differentiate it from other anemia's are present and include maxillary and mandible hyperplasia, reduced sinuses, displacement of maxillary dental structure, over bite, and generalized osteopenia (Lagia, 2006). Hyper transfusion and regular chelation therapy have allowed improved survival in patient with thalassemia major despite medical advances, growth failure and hypogonadism remain significant clinical problems in these patients. In adolescence disproportionate truncal shortening is due to platyspondyly resulting from a combination of factors like hemosiderosis desferrioxamin toxicity or deficiency of trace element (Louis, 2008).

Typical radiographic patterns in the skull included widened diploic space, atrophic especially outer Tables and in some patients, the hair on end pattern. In the ribs, bulbous expansion of the posterior and anterior segments and the rib within rib patterns were observed. As for the spine coarse trabecular arrangement was seen. The "cob web" pattern was seen in the pelvis and finally the lack of the normal concave out line was observed in the long bones (Orzincolo, 1994). Premature fusion of the physes in the tubular bones is a finding which occurs in 10-15% of children with thalassemia major usually after the age of 10 years and most frequently in the proximal humors and distal femur. Such fusion occurs most commonly in patients in whom treatment is delayed and transfusion is not performed until late in childhood or adolescent it may be unilateral or bilateral in distribution.

In the humors, varus deformity is characteristic. Its pathogenesis is probably due to marrow hyperplasia, resulting in trabecular rarefaction and cortical thinning and perforation (De Roeck, 2003). Degenerative arthro-pathy may be the first manifestation of primary hemochromatosis which is seen by MRI. The prevalence of minimal fluid surrounding the scaphoid bone in MRI was (23.3%) which was a novel and significant finding. Other interesting changes included hypo signal intensity (T1and T2) in carpal, metacarpal, radius, and ulna bones. This imaging study can be used for accurate detection of hemochromatosis in joints of thalassemia patients (Karimi, 2007). Cardiac T2 magnetic resonance identifies patients at high risk of heart failure and arrhythmia from myocardial siderosis in thalassemia major and is superior to serum ferritin and liver iron. Using cardiac T2 for early identi-fycation and treatment of patients at risk is a logical means of reducing the high burden of cardiac mortality in myocardial siderosis (Kirk *et al.,* 2009). Hemochromatosis is identified radio graphically as marked increased hepatic attenuation compared to the spleen in the absence of IV contrast, a characteristic appearance is also seen on MRI, with diffuse marked absent signal on both T1 and T2- weighted images. Increased bilirubin production can lead to gallstones and cholecyctitis. (Roberto Maladonado, 2000) Extramedullary hematopioesis, hemosiderosis, and cholelithiasis are among the non–skeletal manifesta-tion of thalassemia Hypoparathyriodism is one of the most important endocrine complications of thalassemia major. By CT of the brain, Intracranial calcification was present in 54.2% of beta – thalassemia patients with hypoparathyriodism. The most frequent sites of calcification were basal ganglia and frontoparietal areas of the brain. Thalami, internal capsule, cerebellum and posterior fossa were other less frequently calcified regions of the brain (Karimi *et al.,* 2009).

Desferrioxamin-induced bone dysplasia: With provision of the modern regime of regular transfusion and desferioxamin chelation, desferioxamin-induced bone dysplasia was a much more frequently detected radiographic abnormality in beta-thalassemia major than radiographic features owing to medullary expansion. In plain film Osteoporosis, as indicated by thinned metacarpal cortices, remained a frequent feature irrespective of status of skeletal dysplasia. The changes due to the desferioxamin induced bone dysplasia include metaphyseal sclerosis in long bone, irregular sclerosis at the costochondral junction and platyspondyly (Chan *et al.,* 2002) Metaphyseal irregularity and abnormal vertebral body were seen in two of five children of thalassemia major who begun on a regimen of hyper transfusion and chelation with desferioxamin before the age of 3 years findings on radiographs included flattening of the thoracic and lumber vertebral bodies, Circumfrential metaphyseal osseous defects, sharp zones of provisional calcification and widened growth plates (Brill, 1991) Desferioxamin induced bone dysplasia is associated with height reduction and can be seen in patients receiving desferioxamin chelation therapy at a doses of less than 50 mg \kg \day. Awareness of the diagnosis is of importance as reduction of the dose may improve bone growth (Chan, 2000) The flattening of the vertebral bodies may be due to suppression of intramedullary hematopioesis by a high transfusion regimen.The reduced intravertebral pressure due to disturbed hemopoiesis could cause weight – bearing and other biological stresses to provoke a reduction in vertebral body height (Carlo Orzincolo, 1994).

Management of thalassemia major: Treatment of thalassemia major includes regular blood transfusion, iron chelation and management of secondary complications of iron over load. In some circumstances, spleen removal may be required. Bone marrow transplantation remains the only definitive cure currently available. Prognosis for individual with B-thalassemia has been improved substa-ntially in the last 20 years following recent medical advances in transfusion, iron chelation and bone marrow transplantation therapy. However, cardiac disease remains the main cause of death in patients with iron overload (Galanello, 2010) The thalassemias are likely to benefit in the future from specific gene therapy. There are also important advances in genetic counseling based on result of early fetal diagnosis (Stanley, 2005).

Aims of the study

- To study the radiographic skeletal changes in transfusion dependent thalassemic patients attending thalassemic center in Ibn Al -Atheer Children Teaching hospital in Mosul and to correlate these changes with age.
- To asses growth retardation in those patients clinically by using normal growth charts comparing them with our records of weights and heights.

Patients and methods: Five hundreds β-thalassemia major patients were included in this prospective study who are attending thalassemia center in Ibn-Alatheer pediatric hospital in Mosul for regular blood transfusion from August 2009 to October 2010. They are (275) males and (225) females. A history was taken from patients and their relatives including: name, age, residence, age at diagnosis, onset and number of blood transfusions, age of starting desferioxamin and the dose of the drug, frequency of blood transfusion per month. Patients were subjected to complete physical examinations and measuring body weight and height. The body weight of children below two years of age have been measured by using Baby scale / Seca 725 Vogel and Halke Germany, body length was measured in recumbent length using Shorr Board U.S.A. productions 17802 shotly Bridge place Olney, Maryland 20832. For children above two years of age using (Fazzini weighing and height measuring devised, Italy). The patients height and weight were compared with standard growth chart curve height for age and weight for age obtained from the national center for health statistics (NCHS) in order to asses the patients growth percentile.

Estimation of Hemoglobin concentration in g\100 ml done,2ml of blood sample was collected in E.D.T.A. container of 2.5 ml size to perform the following hematological investigations within one hour of sampling :Hb, reticulocyt, and blood film. Estimation of hemoglobin concentrations by Symex device model KX 21 N Japan serial no. A9682 (2007) was performed. All patients diagnosed as B- thalassemia major by using VARIANT hemoglobin testing system(Bio-Rad Diagnostic Group, Hercules, CA Milano, Monchen and results with predominant HbF. Patients were divided into two groups to reduce the effects of radiations on these tired patients :200 patients taking for them skull X-ray lateral view and X-ray of the left hand and fore arm,300 patients taking for them chest X-ray PA view. X-rays were taken to the patients using Shimadzu X-ray machines (Shimadzu corporation-Nishiuokyo-Kuwabaracho. Nakagyo-Ku.Kyoto 604-8511 Japan. and at optimal kv and mass and those bad quality X-ray films are either repeated at the time or discarded from the materials

under study. All these X-rays are taken once at time of admission and to minimize the exposure of the patients to radiation We didn't taken for example X-ray of para nasal sinuses, pelvis, feet, femur and we satisfied with those X-rays, mentioned above. The statistic method used S PS S (Chi square test and P Value).

RESULTS

Age distributions in 500 B-thalassemia major patients, their age group range from (> 1 – 32) year. 132 patients fall in the age group > 1 – 5year which represent (26.4%) of the total number of the studied patients. 147 patients fall in the age group (6-10) year and represents (29.4%) of the total number of the studied patients. 122 patients in the age group 11-14 years and their percentage from the total number of patients (24.4%). 99 patient were in the age group (15-32) years which represents (19.8%) of the total number of patients. The largest group of patients was in the range 6-10 years,then the percentage declines because of complications and end by death, the age range distributions in transfusion dependent B-thalassemia major shown in the Table 1 & Fig. 1(Histogram).
Two hundred twenty five patients were females which represent (45%) of the total number of patients and 257 were males (55%), male to female ratio 1.2:1 as shown in Table 2. Hemoglobin level was done for each patient before taking blood transfusions, the patients were divided into two groups: 50 patients (10%) their Hemoglobin level ranges from 4-6 g\dl which indicates sever anemia and 450 patients (90%) their Hemoglobin level was between 7-9 g\dl which indicates mild to moderate anemia this is shown in Table 3, Fig. 2 (Pie chart).
Complains of patients to desferoxamine 325 patients (65%) out of 500 patients had no complains and 175 patients (35%) had good complains to the drugs, as shown in Table 4, Fig. 3(Pie chart).

Five hundred patients were studied, (200) of them had skull x-ray lateral view, x-ray of the left hand and forearm, to see the effects of anemia and the blood transfusions on those patients. 300 patients was taken for them chest X-ray PA view to study the effects of thalassemia on the ribs and the heart. we divided the total number of patients into two groups to decrease the effects of radiations on those tired patients. Hand bone changes studied according to their age group: (> 1 – 5) years, 13 patients (6.5%) had abnormal hand changes which includes widening of the bones and thin cortex only. 28 patients (14%) had no abnormality seen. In the age group 6-10 years 21 patients (10.5%) had abnormal changes which include thinning of the cortex, the bone becomes fusiform shape, osteoporosis and localized lucency, and 45 patients (22.5%) show no abnormality. In the age group 11-14 years 12 patients (6%) had abnormal changes 37patients (18.5%) had no abnormal changes seen. In the age group 15-32 year 16 patients (8%) had abnormal hand changes and 28 patients (14%) had no abnormality in the hand bone seen. From the total numbers of the patients (31%) had hand bone changes and (69%) had no abnormal bone changes was seen, and the highest percentage located in the age group 6-10 years, the P-value by Chi- square test was 0.661 which is non significant as shown in Table 5, Fig. 4 (Pie chart) & Fig.5 a (x-ray of hand). Long bone of the fore arm (radius &ulna) shows variable degree of thinning of the cortex with increase medullary spaces were noted in 58 patients (29%) of the total number of cases, and 142 patients (71%) had no bone changes and the highest percentage of the abnormal changes in radius &ulna fall in the age group 11-14 years.

Table 1. Age distribution of B-thalassemia major patients

Age	Patients no.	% out of 500 Patients
> 1 - 5 years	132	26.4
6 - 10 years	147	29.4
11 -14 years	122	24.4
15 -32 years	99	19.8
Total	500	100

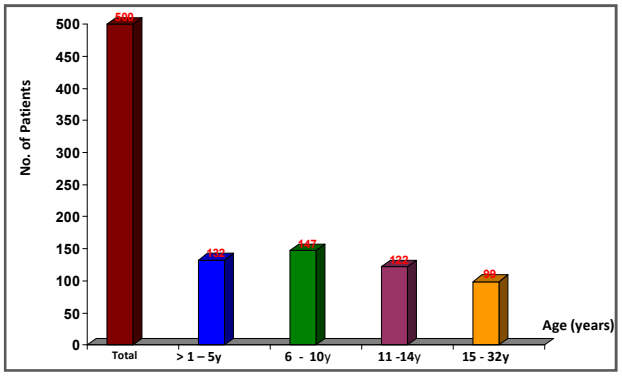

Fig. 1. Histogram of age distribution of B-thalasemia major patients

Table 2. Gender distribution of β - thalassemia major patients out of 500 patients

Sex	Patients. no.	Percentage %
Male	275	55
Female	225	45
Total	500	100

Table 3. Show the Hemoglobin level of the studied patients out of 500 patients

Hemoglobin (gm/dl)	Patient. No.	Percentage%
4 - 6	50	10
7 - 9	450	90
Total	500	100

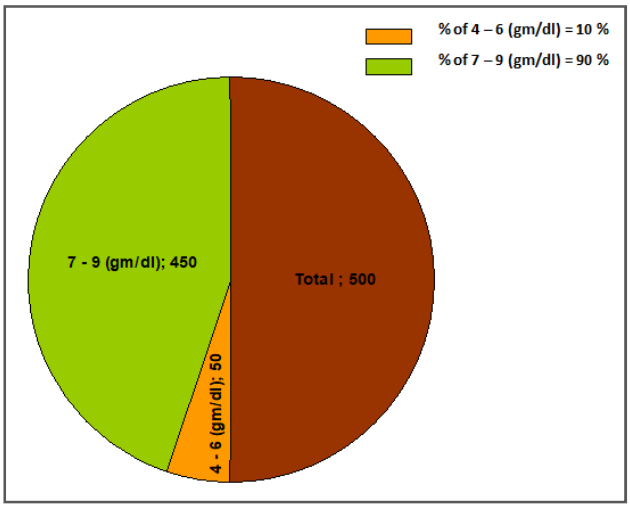

Fig. 2. Pie chart show the Hemoglobin level of the studied patients out of 500 patients

In the age group > 1 – 5 years, 9 patients (4.5%) had abnormal long bone changes and 31 patients (15.5%) had normal long bone. In the age group 6-10 years 15 patients (7.5%)had abnormal radius & ulna and 49 patients (24.5%) had no abnormal changes. In the age group 11-14 years 30 patients (15%) had no changes and 21 patients (10.5%) had abnormal bone changes.

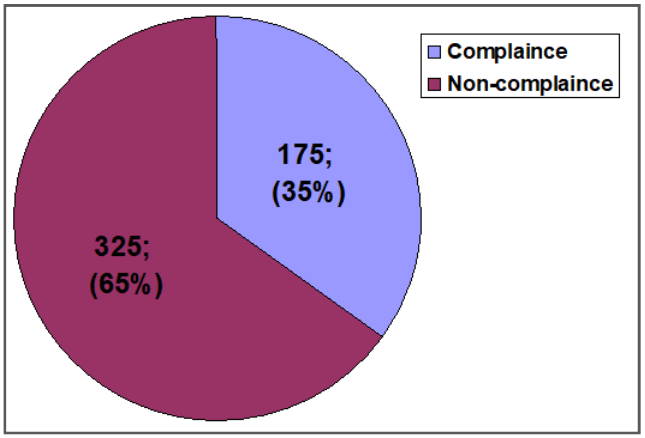

Fig. 3. Pie chart of compliance of patients to desferoxamine

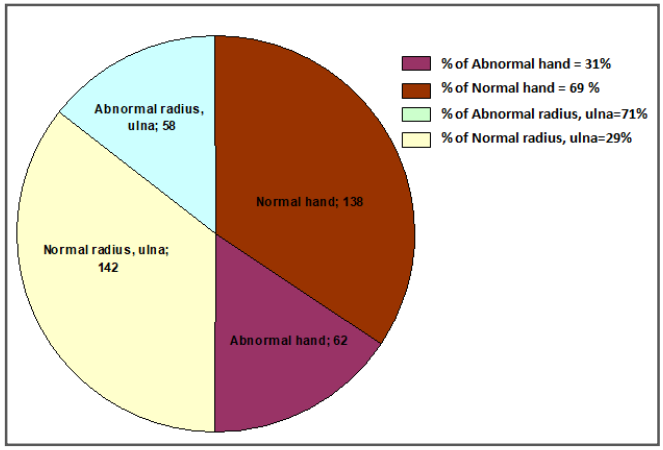

Fig. 4. Pie chart show the hand bone, radius and ulna(long bone) changes in the 200 patients out of 500 patients according to their ages

In the age group 15-32 years 32 patients (16%) had no changes and 13 patients (6.5%) had abnormal radius and ulna changes. P-value by Chi-square test: 0.141 which's non significant. as shown in Table 5, Fig. 4 (Pie chart) & Fig. 5 b (x-ray of hand and fore arm).

Skull changes in 200 patients studied in relation to their age group: > 1 – 5 years: 13 patients (12%) had abnormal skull radiological :10 of them (5%) had widening of diplio with thinning of outer table and 3 patients (1.5%) had widening of frontal region of skull only 15 patients (8%) had normal skull bone. In age group 6-10 years 50 patients (28%) had abnormal skull :47 patients (23.5%) of them had widening of the diplio and thinning of the outer Table and 2 (1%) had widening of the frontal region of the skull and one patient (0.5%) had enlargement of the diplio with hair -on-end changes. In the age group 11-14 years 7 patients who represent (4%) of the total number of the studied patients had normal skull bone, 45 patients (23%)had abnormal skull changes : 39 patients of them (19.5%) had thinning of the outer table of skulls and widening of diplio and 4 patients (2%) had widening of frontal Table and 2 patients(1%)had enlarged diplio with hair-on-end appearance and 7 patients (4%) had normal skull bone.In the age group 15-32 years 33 patients (19%) had abnormal skull changes: 30 patients (15%)had widening of diplio and thinning of outer Table,2 patients (1%) had widening of frontal region of skull, one patient(0.5%) had enlarge-ement of diplio with hair-on-end appearance while 27 patients (13%patients) had normal skull bone. From the 200 patients were done for them skull x- ray 141 patients (71%) had abnormal skull changes from them 126 patients (63%) had widening of diplio with thinning of the outer Table, enlargement of diplio with hair-on-end appearance find in 4 patients (2%), and widening of frontal region of skull in 11 patients(5.5%) and Skull radiological changes in the studied patients. The P-value done by Chi-square= 0.001 which is significant, as shown in Table 6, Fig. 6 (Skull x-ray).

The rib changes were studied in 300 patients who were taken for them chest x-ray according to their age group. In age range > 1 – 5 years 25 patients (8.3%) had abnormal rib changes, 20 patients (6.67%) out of the 25 patients had widening of the ribs and 23 patients who represent (7.67%) had osteoporosis, 18 patients had localized lucency (6%), 10 patients (3.3%)had sub cortical lucency, no rib within rib appearance seen in this age group and no any case of thoracic extramedullary hematopioesis is noticed in the studied patients. Patients with normal ribs were 45 who represent (15%) of the total number of patients with chest X-ray. The age group 6-10 years consist of 45 patients who represent (15%) of the total number had abnormal rib changes, 40 patients(13.3%) had widening of the ribs and 45 patients which represent (15%) had osteoporosis and 29 patients (9.67%) had localized lucency,25 patients(8.3%) had sub cortical lucency, 4 patients (1.3%) had rib –with in ribs appearance. 20 patients (6.7%) had no abnormal rib changes. In the age group 11-14 years 65 patients (22.67%) showed abnormal rib changes: 55 patients (18.3%) had widening of the ribs, 65 patients (21.67%) had osteoporosis, 53 patients (17.67%) had localized lucency, 40 patients (13.3%)had sub cortical lucency and 7 patients (2.3%) had rib-with-in rib appearance and 15 patients (5%) only had no abnormal rib changes.

In the age group 15-32 year 80 patients (26.67%) showed abnormal rib changes, 74 patients(24.67%) had widening of the ribs and 80 patients (27%) had osteoporosis, 68 patients (22.67%) had localized lucency and 37patients (12.3%) had sub cortical lucency, 9 patients (3%) had rib-with-in rib appearance, only 5 patients (1.67%) had normal ribs. From the total number of the chest X-ray taken 300, 215 patients (72%) showed abnormal rib changes: 189 patients (63%) had rib widening only, 213 patients (71%)had osteoporosis,168 patients (57%) had localized lucency,112 patients (36.3%)had sub cortical lucency and 20 patients (6.67%) had rib within rib appearance and 85 patients (28%) showed no rib changes. P-value by Chi –square test =0.001 which's very high significant, as shown in Table 7, Fig. 7 (Chest x-ray). In the chest x-ray of the studied patients we divided the patients with cardiomegally according to the age group: In the age group > 1 – 5 years 32 patients (10.67%)had cardiomegally and 22 patients (7.3%) had normal heart shadow. In the age group 6-10 year 48 patients (16%) had cardiomegally while 30 patients (10%) had no cardiomegally. In the age group 11-14 years, 45 patients (15%)had cardiomegally while (39) patients (13%) had no cardiomegally. In the age group15-32 years (55) patients (18.3%) had cardiomegally while (29)patients (9.6%) had no cardiomegally. From the total number 300 patients who were take for them chest x ray 180 patients (60%) had cardiomegally and 120 patients (40%)had no cardiomegally, the P-value was 0.460 (non significant) as shown in Table 8, Fig. 8 (Histogram) & Fig. 9 (Chest X-ray).

Other complications seen in the studied patients: delayed puberty 145 patients (65.6%) from the 221 patients who represent the age group 10- 14 years and age group 15-32 years, diabetes in 56 patients (11.2%), hypoparatyriodism 54 patients (10.8%), hepatitis C virus infection 66 patients

Table 5. Show the hand bone, radius and ulna(long bone) changes in the 200 patients out of 500 patients according to their ages

Age range	pt.no. Normal Hand	%	pt.no. Abnormal hand	%	Hand dysplastic changes	pt.no. normal radius, ulna	%	pt. no. abnormal radius& ulna	%	Long bone dysplastic changes
> 1-5 year	28	14	13	6.5	-	31	15.5	9	4.5	-
6 -10 year	45	22.5	21	10.5	-	49	24.5	15	7.5	-
11-14 year	37	18.5	12	6	-	30	15	21	10.5	-
15 -32year	28	14	16	8	-	32	16	13	6.5	-
Total 200	138	69	62	31	-	142	71	58	29	-
P*-value	0.661				0.141					

Table 6. Shows relation of age to skull changes

Age	pt. no. with normal skull & %	pt. no. with abnormal skull & %	Widening of diplio & thinning of outer Table & %	Widening of frontal region & %	Enlargement of diplio with hair-on-end appearance & %
> 1-5 year	15	13	10	3	0
	8 %	12 %	5 %	1.5 %	
6-10 year	10	50	47	2	1
	5 %	28 %	23.5%	1 %	0.5 %
11-14 year	7	45	39	4	2
	4 %	23 %	19.5%	2 %	1 %
15-32 year	27	33	30	2	1
	13 %	19 %	15 %	1 %	0.5 %
Total	59	141	126	11	4
200	29 %	71 %	63 %	5.5 %	2 %
P* value	0.001				

Table 7. Show the ribs changes in the studied patient according to their ages

Age Range	pt. with normal ribs & %	pt. with abnormal ribs & %	Rib widening & %	Osteoporosis & %	Localizes lucency & %	Subcortical lucency & %	Rib-within-rib & %
> 1-5 year	45	25	20	23	18	10	0
	15%	8.3%	6.67%	7.67%	6%	3.3%	0 %
6 -10 year	20	45	40	45	29	25	4
	6.7%	15%	13.3%	15%	9.67%	8.3%	1.3%
11 – 14 year	15	65	55	65	53	40	7
	5%	22.67%	18.3%	21.67%	17.67%	13.3%	2.3%
15-32 year	5	80	74	80	68	37	9
	1.67%	26.67%	24.67%	27%	22.67%	12.3%	3%
Total	85	215	189	213	168	112	20
300	28 %	72 %	63%	71%	57%	36.3%	6.67%
P* value	0.001 (Very high significant)						

* Chi-square test was used with df = 3. P < 0.05 significant P > 0.05 non-significant

Table 8. Show the cardiomegally in the studied patient according to their ages

Age Range	pt. with cardiomegally	Percentage %	pt. with out cardiomegally	Percentage %
> 1-5 year	32	10.67	22	7.3
6 -10 year	48	16	30	10
11 - 14year	45	15	39	13
15-32 year	55	18.3	29	9.6
Total	180	60	120	40
300				
P* value		0.460 (Non-significant)		

Table 9. Complication of β-thalassemia patients

Complication	No. of patients	%
Delayed puberty	145	65.6
Diabetis mellitus	56	11.2
Hypoparathyroid	54	10.8
Hepatitis C virus infection	66	13.2
Cholelithiasis	59	11.8

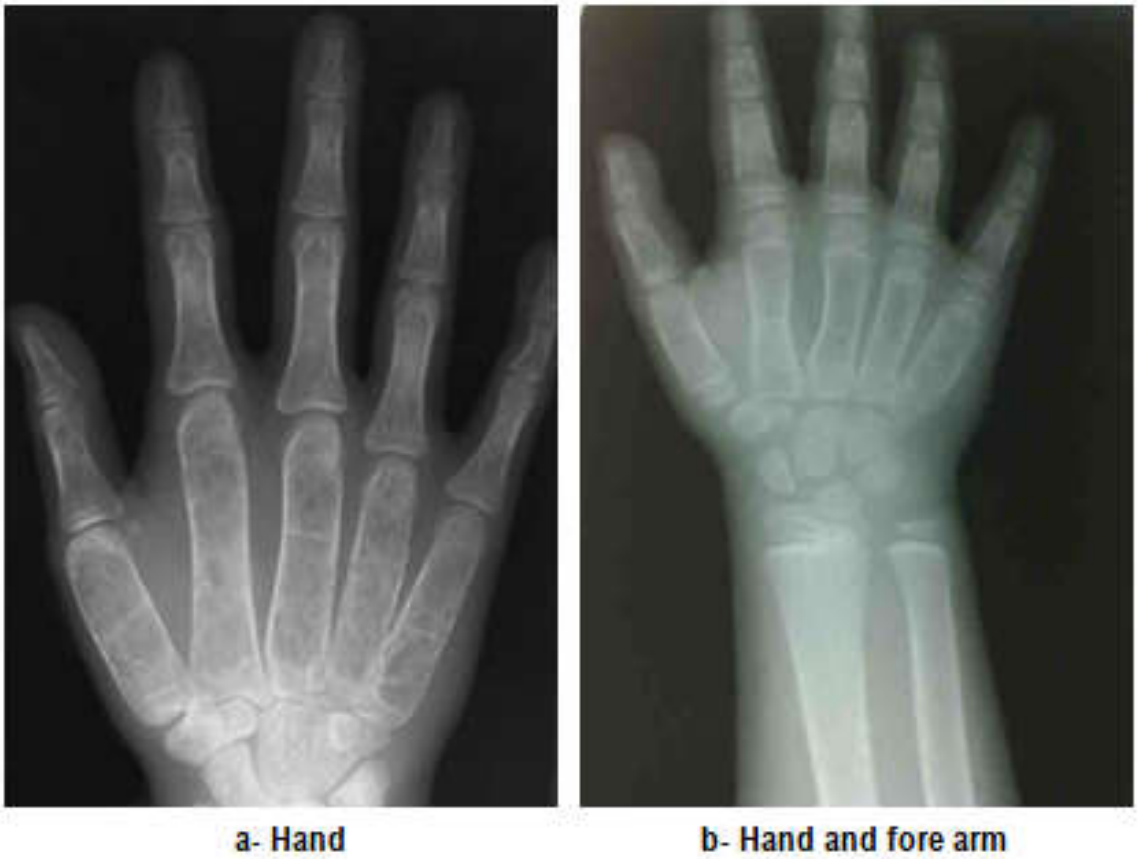

Fig. 5. X-ray of hand (a) and x-ray of hand and fore arm (b) showing trabeculations and cortical thinning in the metacarpals, phalanges, radius & ulna

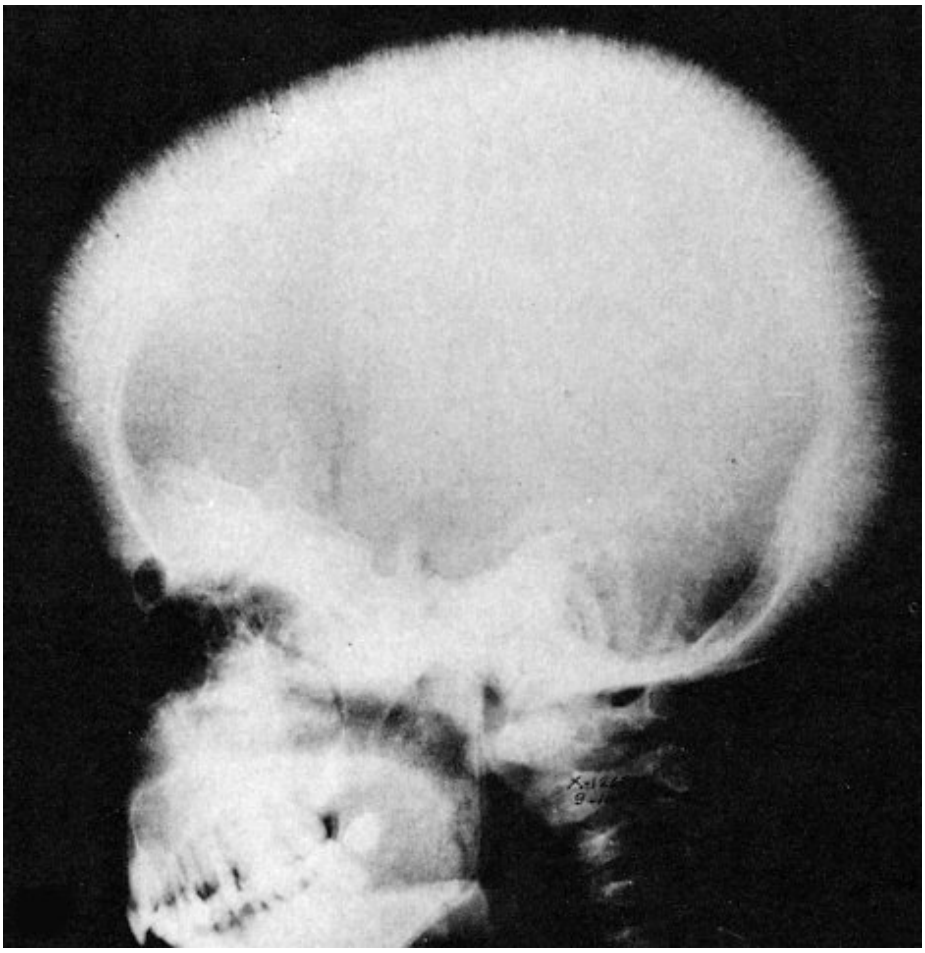

Fig. 6. Lateral skull X-ray showing thickening with hair – on – end appearance

Table 10. Distributions of B-thalassemia major according to their weight centile on growth charts

Age Range	pt. no. Below 5th centile	%	pt. no. 5th-25th centile	%	pt. no. above 25-50th centile	%	pt. no. above 50th centile	%
>1-5 year	28	5.6	45	9	25	5	29	5.8
6-10 year	45	9	67	13.4	32	6.4	23	4.6
11-14year	89	17.8	33	6.6	1	0.20	3	0.60
15-32 year	49	9.8	26	5.2	3	0.6	2	0.40
Total 500	211	42.2	171	34.2	61	12.2	57	11.4
P* value	0.001 (Very high significant)							

Table 11. Distributions of B-thalassemia major patients according to their height centile on growth charts

Age	pt. no. below 5th centile	%	pt. no. 5th-25th centile	%	pt. no. above 25th-50th centile	%	pt. no. above 50th centile	%
> 1-5 year	43	8.6	46	9.2	18	3.6	13	2.6
6-10 year	65	13	44	8.8	17	3.4	11	2.2
11-14 year	120	24	24	4.8	11	2.2	0	0
15-32 year	52	10.4	19	3.8	10	2	7	1.4
Total 500	280	56	133	26.6	56	11.2	31	6.2
P* value	0.001 (Very high significant)							

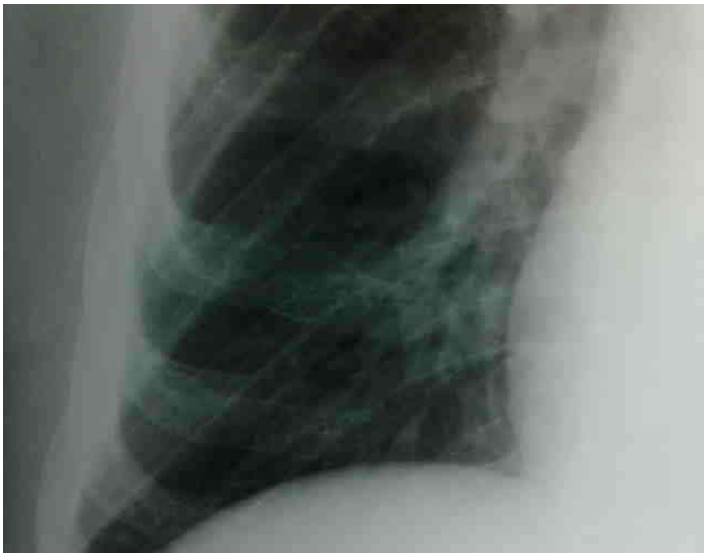

Fig. 7. Chest x-ray showing rib with in a rib the central areas of increased density seen in most of the ribs

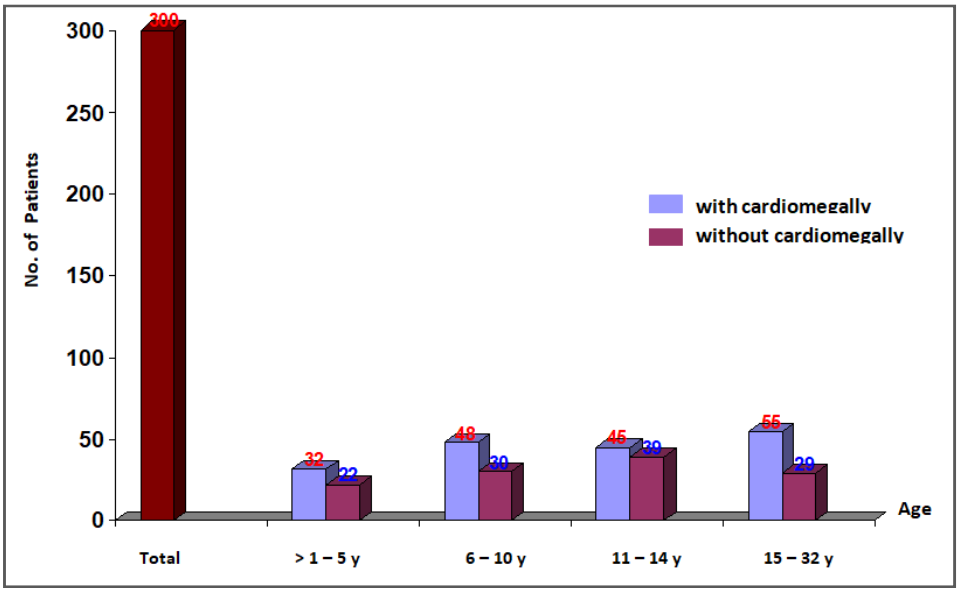

Fig. 8. Histogram showing the cardiomegally in the studied patient according to their ages

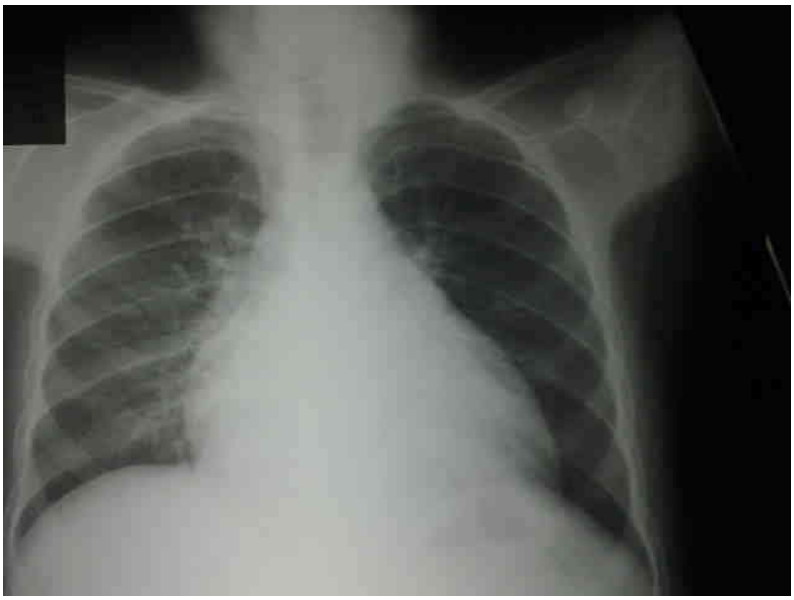

Fig. 9. Chest X-ray showing cardiomegally in β-thalassemia major patient

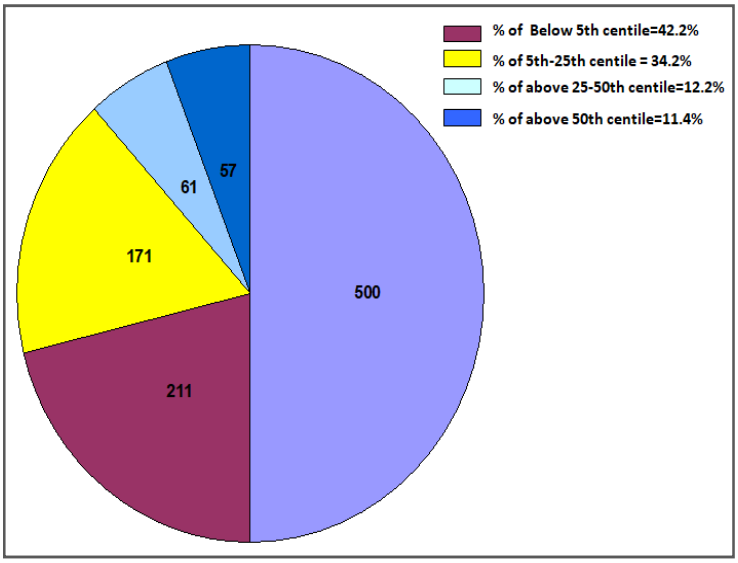

Fig. 10. Pie chart of distribution of β-thalassemia major according to their weight centile on growth charts

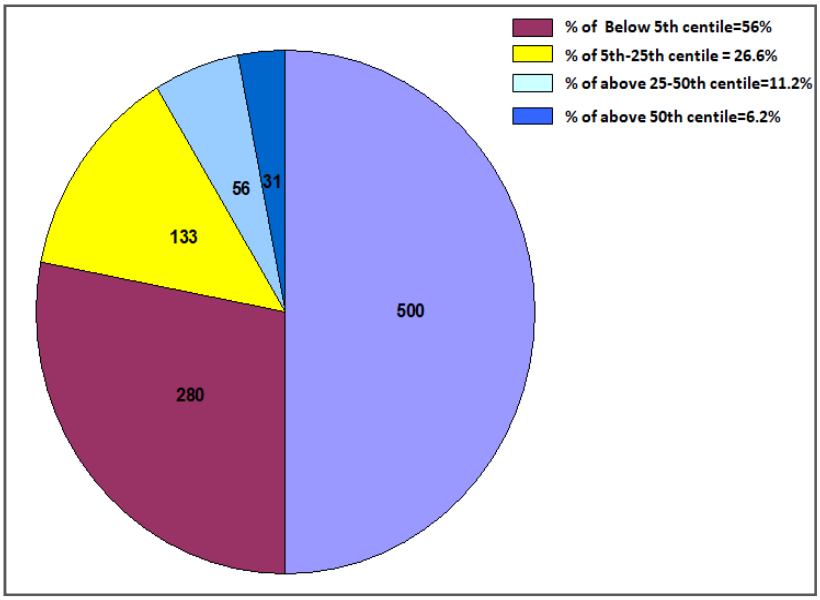

Fig. 11: Pie chart of distribution of β-thalassemia major patients according to their height centile on growth charts

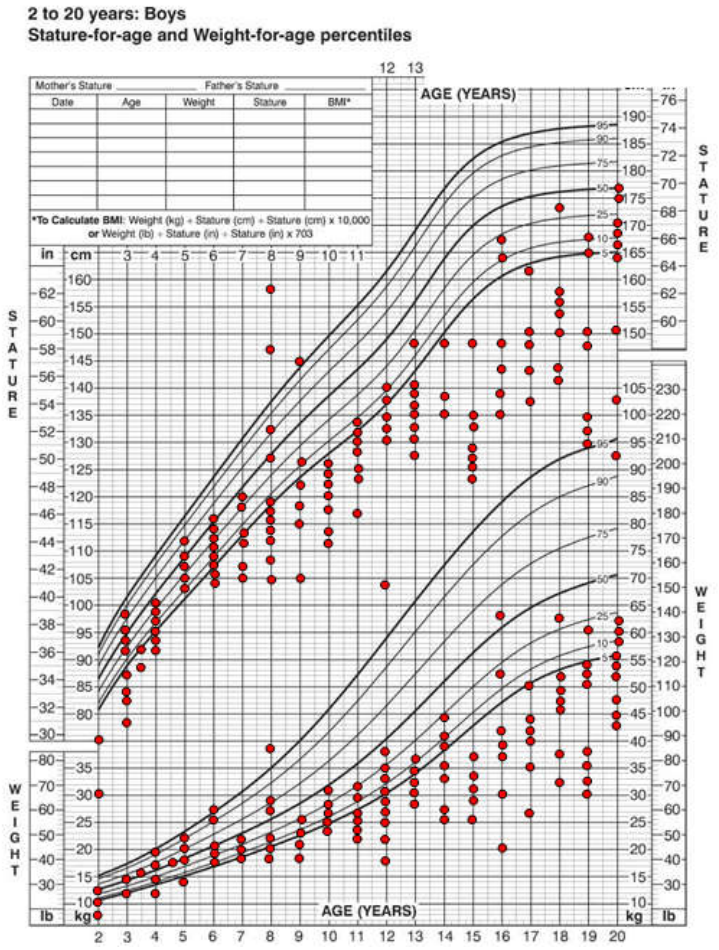

Fig. 12. Distributions of β-thalassemia major according to their weight & height centile on growth charts (In boys)

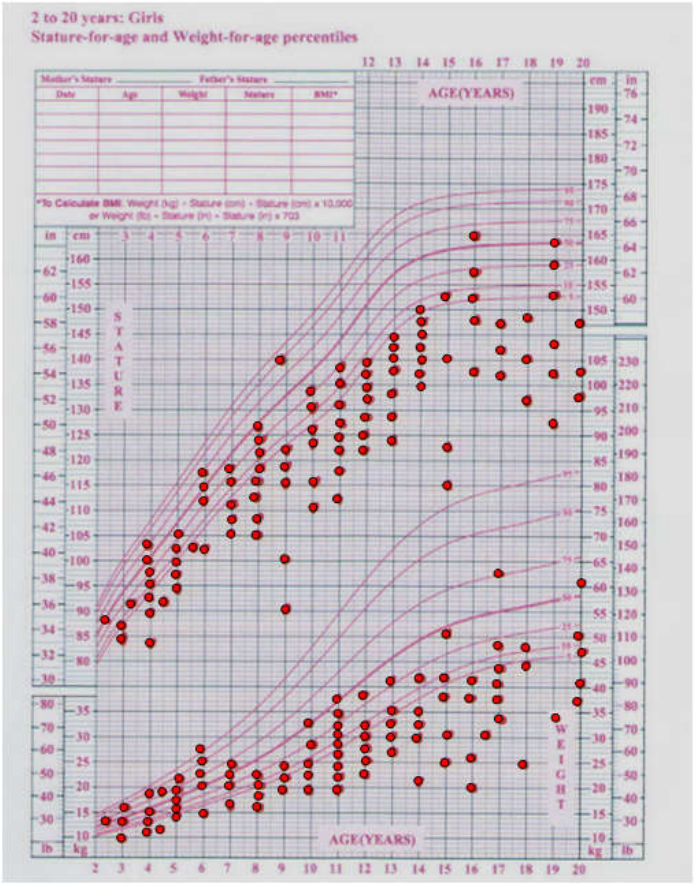

Fig. 13. Distributions of β-thalassemia major according to their weight & height centile on growth charts (In girls)

(13.2%), cholelithiasis in 59 patients (11.8%) of the total number of the patients, as shown in Table 9. Effects of anemia in thalassemic patients on their growth studied by using the W H O growth charts for weight and height.

- Weight for age of the age group > 1 – 5 year 28 patients out of the total number 500 patients, (5.6%) fall below the 5th centile (which regarded as sever weight for age retardation.
- In the age group 6-10 years 45 patients(9%) fall below 5th centile which represent sever retardation for their age group.
- In age group 11-14 years 89 patients (17.8%) fall below 5th centil.
- In the age group 15-32 years 49 patients (9.8%) their weight fall below the 5th centile.

From the total number of patients under study 500, 211 patients (42.2%) fall below 5th centile and 171 patients (34.2%) fall on the 5th -25th centile, and 61 patients (12.2%) fall in the rang above 25th -50th centile and 57 patients (11.4%) were located above 50th centile. The P-value by Chi-square test= 0.001(very high significant), as shown in Table 10, Fig. 10 (Pie chart), Fig 12 (growth chart in boys) and Fig. 13 (growth chart in girls). Height retardation was studied on those patients by putting their height on the standard height for age growth chart. According to their age group. In the age group. 1 - 5 years 43 patients (8.6%) fall below 5th centil which indicates sever height retardation. In the age group 6-10 years 65 patients (13%) had their height fall below 5th centile. In the age group 11-14 years 120 patients (24%) their height fall below the 5th centile. In the age group 15-32 year 52 patients (10.4%) of the total number fall below the 5th centile. 280 patients out of the total 500 patients (56%) had sever height retardations for their age, 133 patients (26.6%) fall between 5th -25th centile, 56 patients (11.2%) fall in the above 25th-50th centile,31 patients(6.2%) fall above the 50th centile. as the age progress, the disease progress and the disease affects the height of those studied patients. P-value =0.001 very high significance), as seen in Table11, Fig. 11(Pie chart), Fig. 12 (growth chart in boys) and Fig. 13 (growth chart in girls).

DISCUSSION

In this series the discussion of the results concerning the radiological skeletal changes in thalassemia major patients and the effects of blood transfusion and chelation therapy on the bone evaluated by using x-Ray of the hand,skull,chest, in comparison with other authors in the world is as follow: The age of developing the skeletal changes : study done by M. Agouzal, A. Arfaoni, A. Quyon, and m.kattab (2010) (Agouzal, 2010) they found the patients their age group 6-10 years are the largest age group who affected by the disease beyond 15 years the number of patients decreases. In this series the peak age incidence of patients 6-10 years which represent 29.4 % of the total number of the patients Table 1, Fig. 1 (Histogram). the result was parallel to the result of the previous authors This can be explained by the fact that if children are not transfused they will die before the age of 6 years so this age group small and if they are transfused and non-chelated they will die before the age of 20 years this due to either to phenotypic severity of the disease or to the very poor management protocol. The distribution of patients according to their sex: study done by M. Agouzal, A. Arfaoni, A. Quyon, and m.kattab (2010) they found there is no significant difference between male and female (1:1) regarding the occurrence of the disease. In this series shows male to female ratio1.2 : 1, Table 2. This result parallel to the above author study. The explanation of no significant difference between male and female regarding the occurrence of the disease because its autosomal recessive disease occur equally in both male and female. The effectiveness of the transfusion program : Neeraj Shah, Anupa Mishva, Dhaval Chauhay C Vova, N R Shal (2010) [37] they found (53.5%) were under transfused (mean Hb less than 10gm/ dl). In this series: the Hb of the patients is 10% was between 4-6 gm/ dl and 90% is between 7-9 gm/ dl that's to say the sum of the treated patients will be 100% below 10gm/ dl, Table 3, Fig. 2 (Pie chart). this result is much higher than result found by the above study. This indicates that our patients not treated by hyper transfusion program and low transfused patients this because poor compliance of patient for blood transfusions in addition to being anemic and stressed and cache tic, the characteristic osseous changes appear. Regarding compliance of patient to chelating drug : study done by M. Agouzal, A. Arfaoni, A. Quyon, and M. Kattab (2010) 27% of patients were not compliant with desferioxamin and a (Girot *et al.,* 2006) study were 20-40% of studied patients were not compliant with desferioxamin. In this series 65% of patients were not compliant on desferioxamin table 4, this result is higher than the above author study because the patients in this study not cooperative to take the desferioxamin because this drug taken subcutaneously for five day \week and painful injection. The effects of the blood transfusions and chelation therapy drug (desferioxamin) studied on bone of the hand and the long bone : study by Papageorgion et al (2002) that showed 91% of hyper transfused patients with thalassemia major develop osteoporosis and 70% develop cortical thinning and Deve nejoul *et al.* (2002): observed thin metacarpal cortices related to increased resorbtion of bone. In this series 31% of patients had hand bone changes which include thinning of the bones cortex and the bone become fusiform shape and osteoporosis with localized lucency and The changes in the radius & ulna: 29% had variable degree of thinning of the cortex with increase of medullary spaces. The P-value by Chi- square test was 0.661 for the hand changes and the P-value by Chi-square test: 0.141 for the ulna and radius changes which are non significant, Table 5, Fig. 4 (Pie chart). This result lower than the above authors studies, because those patients take blood transfusion and this decrease the bone changes.

Deferoxamine –induced dysplastic changes in long bone and hand: Garofalo *et al.* (2002) reported 85% of skeletal dysplasia typically this complication involves the metaphysis of the distal radius and ulna. In this series we had no any case of desferroxamine –induced dysplastic changes in hand and long bone, Table 5. There is very high difference between this study and the above author study because desferioxamine compliance is low so the toxicity on the bone not present. The skull radiological changes: In author Wiston study (2001) the skull changes increased in severity as the increasing age and 8.3% had hair on end appearance. In this series (2%) had enlargement of diplio with hair- on- end appearance from the studied patients. the P-value done by Chi-square= 0.001 which is significant, Table 6, Fig. 6. This result is higher than the above author result because our patients are under transfused so the skeletal changes become more sever. The rib changes: The authors Ersi Voskari don and Evangelos Terpos study (2004) they found 71% had osteoporosis. In this series 71%

had osteoporosis of ribs, changes increased with increasing age. P-value by Chi–square test =0.001 which's very high significant, Table 7, Fig 7 this result in agreement with the above author study. This result is high because the studied patients are under transfused so the osteoporosis represents an important cause of morbidity in adult patients with thalassemia which is multifactorial causes. Cardiomegaly found by chest X-RAY: The study of Kirk *et al.* (2009), who found myocardial siderosis resulting in heart failure remain the major cause of death (50-70%), and Agouzal *et al.* (2010) study where the percentage of heart failure is 6%, Gamberini et al study (2009) where the percentage was (69%). In this series the percentage of cardiomegaly was 60%. P-value was 0.460 (non significant), Table 8, Fig. 8. This result in agreement of Kirk et al and Gamberini et al study and much higher than M. Agouzal study. This high result in the studied patients due to iron over load and cardiac hemosiderosis (Deborah Rund, 2005). Regarding other complications: study of M. Agouzal, A. Arfaoni, A.Quyon, and m.kattab (2010): delayed puberty represent (63%), diabetes mellitus (7%), hypoparathyriodism (4.6%), Mehri Ghafourian Boroujerdnia et al (2009) found Hepatitis C virus infections was 28.1%. In this series Hepatitis C virus infections represent (13.2%), delayed puberty represent (65.6%), diabetes mellitus (11.2%), hypoparathyriodism (10.8%), Table 9. The diabetes mellitus, delayed puberty, hypoparathy-riodism those complication higher in these patients than the above authors study because the patient not compliant to desferroxamine and develops hemosiderosis to the endocrine glands, Hepatitis C virus infections is lower than the above author study because repeated blood transfusions of properly screened blood.

Cholelithiases: found by Por tincasa p. e t al study(2004) [40] was 56% and the study don by A.G.Kalayci et al the percentage 11.8% (1999). In this series Cholelithiases represent 11.8% of the studied patients Table 9 which is lower than what found by Por tincasa. et al and the same of A.G. Kalayci et al percentage. The risk of cholelithiasis increases after the age of 10 years so due to the longer survival of patients with B- thalassemia the problem of cholelihiasis is becoming more frequent because o f chronic hemolysis. Regarding the effects of thalassemia major on the growth: The author Anita Saxena (2003) found (20%)of the patients their weight growth curve and height growth curve below 5th centile and gradual increases in height and weight till 11 years in boys and till 8 years and 10 years for the both parameter in girls. In this series patients weight growth curves (42%) of patients below 5th centile and 56% their height below 5th centile and gradual increase till 7 years for weight and 6 years for height for both boys and girls then the curve declines to fall below the normal curve for their age, P-value by Chi-square test= 0.001 for weight growth chart (very high significant), and P-value =0.001 for height growth chart (very high significance), Table 10,Table 11, Fig.10, Fig 11. In this study the result was higher than what had been found by Anita Saxena study This indicates that our patients are stunted in growth earlier and had sever growth retardation this due to poor compliance of the patient for blood transfusion and desferioxamin. The costochondral junction seclerosis which is the sign of desferioxamin toxicity: Garofalo et al (2002) reported 85% of skeletal dysplasia in his studied group while in this series we did not find any case of costochondral junction seclerosis because patients had poor compliance for the drug in contrary the effect of hemosiderosis on the heart, liver and endocrine system cause serous complication.

The end result of this series the peak age incidence of the skeletal change in the age group 6-10 years same as other authors study,65% had no compliance to desferroxamine which is higher than other authors results. Bone changes is lower than other authors studies (31%hand bone change, 29% long bone changes, 2% had sever skull changes hair on end appearance) except the rib osteoporosis (71%) which's the same as other author results. From the non skeletal complications; 60% cardiomegaly,65.6% delayed puberty,11.2% diabetes mellitus,10.8% hypoparathyriodism these complications higher than other authors studies. Both (13.2%) Hepatitis C virus infections and (11.8%) cholelithiasis lower than other authors studies. 42% weight growth retardations, 56% height growth retardations these complications higher than other authors studies as shown in table 12.

Conclusion

Consequent to what mentioned in this series, the following conclusions:

- Thalassiemia major patients in Mosul center (77%) of them diagnosed during the 1st year of life, this indicates the severity of the disease which is important in producing the boney changes of thalassimia if not properly transfused.
- (90 %) of those patients their hemoglobin before transfusion is between (7 – 9) gm /dl, this mean patients not treated by hyper transfusion program, so the boney changes become more evident, (our patients under transfused).
- (31 %) of patients had hand changes: thinning of bone cortex, bone become fusiform, osteoporosis.
- (29 %) had long bone changes (radius, ulna): thinning cortex with increase medullary spaces, which is highest in the age group (11–14) years, the percentage declines in older age group because of death of those patients due to complications.
- (71 %) of patients had skull changes and these changes and its severity increase with age.
- (71 %) of patients had osteoporosis of ribs which represents an important cause of morbidity in adult thalassimic patients.
- Changes of desferroxamine induced bone dysplasia were not seen in any patient because (65 %) of our patients had poor compliance to use desferroxamine, so its toxicity on the bone not seen in the studied patients.
- The effects of hemosiderosis is due to poor compliance to desferroxamine appear in those patients and in higher percentage than what seen in other studies:
- (60 %) had cardiomegally, (65.5 %) had delayed puberty, (11.5 %) had diabetes mellitus, (10.8 %) had hypoparathyroidism, (13.2 %) had hepatitis C virus infection.
- Cholilithiasis was present in (11.8 %) which was lower than what has been found in other studies because cholilithiasis increased with age and our patients had lower survival rate.
- No any case of extra medullary haematopoesis has been seen in our study because the skeletal feature of thalassimia were ameliorated by frequent transfusion.

- Our patients stunted in growth earlier than other study and the retardation of height more prominent than weight due to poor compliance of our patients for blood transfusion and desferroxamine therapy.

Suggestions

I suggest to use blood hyper transfusion program to supers the effect of anemia on the bones and to use the oral chelating agent which is available in the other country and used to get better compliance of chelation to over com the problem of painful daily subcutaneous injection of desferioxamin and to prevent the problem of hemosiderosis of the liver, heart, endocrine gland.

REFERENCES

Agouzal, M., Arfaoui, A., Quyou A. and Khattab M. 2010. Beta thalassemia major: The Moroccan Experience. *J of Public Health and Epidemiology*, Vol. 2(2), pp. 25-28.

Alireza Fotouhi Ghiam, Alireza Hashemi, Samira Taban Mohammad Reza Bordbar, Mehran Karimi 2010. Beta Thalassemia Minor as a Risk Factor for Suicide and Violence: A failure to Replicate. Psychology vol. 1: pp17-21.

Anita J. Catlin 2003. Thlassemia: The Facts and the Controversies. Pediatrc Ethics. Issues, and commentary vol. 29 page 6.

Anita Saxena 2003. Growth retardation in thalassemia major patients. *Int. J. Hum. Genet*., vol. 3 (4): 237-246.

Asha Shah 2004. Thalassemia Syndromes. Indian J 0f Medical Sciences, Vol. 58 (10): pp 445-449.

Baker H.Al- Awamy 2000. Thalassemia syndromes in Saudi Arabia Meta analysis of local studies. *Saudi Medical J*., vol. 21(1) :pp 8-17.

Bedir E M., Helmy AN., Yakout K., Soliman AT. 2008. Review of radiologic skeletal changes in thalassemia. Pediatric Endocrinol. Rev vol. 7 (1): pp 123-126.

Brill, PW., Winchester, P., Giardina PJ. and Cunningham-Rundles S. 1991. Desferoxamine –Induced Bone Dysplasia in patients with thalassemia major. *AJR* Vol. 156:pp561-565.

Carlo Orzincolo, Giuseppe Castaldi and Pier Nuccio Scutellari 1994. Platyspondyly in treated beta thalassemia. Eur. J. of Radiology, Vol. 18(2): pp129-133.

Chan YL., Pang LM., Chik KW., Cheng JC., Li CK. 2002. Pattern of bone diseases in transfusion–dependent homozygous thalassemia major: Predominance of osteoporosis and desferrioxamine-induced bone dysplasia. Pediatr Radiol, Vol. 37(7): pp 492-497.

Chan, Y. L. 2000. Desferioxamine –Induced long Bone Changes in thalassemic patients. Clinical Radiology, vol. 55(8):pp 610-614.

Chan, YL., Tse HY 2002. Imaging in Thalassemia. JHK Coll Radiol vol. 5: pp 155-161.

Chan, YL., Tse HY. 2002. Imaging in thalassemia. JHK Coll Radiol vol. 5: pp 155-161.

De Roeck, J., Vanhoenacker, F., Gielen, J., De Schepper, A. 2003. Bilateral humeral changes in Thalassemia major. JBR-BTR, vol.. 86 :pp154-155.

Deborah Rund, and Eliezer Rachmilewitz 2005. B-Thalassemia,New England. J. Medicine.vol. 353: (11) pp 1135-1146.

Deborah Rund, Eliezer Rachmilewitz 2005. Thalassemia. *The New England J. of Medicine*,Vol. 353 (11): pp1135-1146.

Ersi Voskaridou, Evangelos Terpos 2004. New insights in to the path physiology and management of osteoporosis in patient with thalassemia. British J of Hematology vol. 127(2): pp 127-139).

Eva Marie Erfurth, Helene Homler, Per-Gunnar Nilsson and Bjorn Kornhall 2004. Is growth hormone deficiency contributing to heart failure in patients with thalassemia major? *European J.of Endocrinology* vol. 151: pp 161-166.

Feng, Z., Sun, E., Lan, H., Zhang, C., Li Q. and Zhu W. 2006. Unrelated donor bone marrow transplantation for B-thalassemia major: an experience from china. *Bone Marrow Transplantation* Vol. 37:pp 171-174.

Gal Renzo anello, rafaella Origa 2010. Beta – Thalassemia. Orphanet Journal of Rare Diseases vol. 5 page 11.

Galanello R., Origa R. 2010. Beta thalassemia. *Orphanet J Rare Dis*., vol. 21(5):sp 11.

Kalayci A. G. et al. 1999. The incidence of gallbladder stones and gallbladder function in beta –thalassemiic children. Acta Radilogica. vol. 40. pp 440-443.

Kamal mansi, Talal Aburjai, Moussa Barqawi and Hamzeh naser 2009. Copper and Zinc in Jordanian patients with B-Thalassemia Major. Research Journal of Biological sciences. Vol. 4 (5): pp 566-572.

Karimi M., Jamalian N., Rasekhi A., Kashef S. 2007. Magnetic resonance imaging (MRI) findings of joints in young beta - thalassemia major patients: fluid surrounding the scaphoid bone :anovel finding, as the possible effect of secondary hemochromatosis. *J Pediatr. Hematol. Oncol*., Vol. 29 (6):pp 393-8.

Karimi M., Rasekhi, AR., Rasekh M., Nabavizadeh SA., Assadsangabi R., Amirhakimi GH. 2009. Hypoparathyriodisim and intracerebral calcification in patients with beta – thalassemia major. Eur J Radiol.vol 27(3):pp481-484.

Kirk, P., Porter, J. B., Tanner, M.A., Taylor, J. Anderson. L.J. 2009. Cardiac T2 Magnatic Resonance for Prediction of Cardiac Complications in thalassemia major. *American Heart Association*. Vol.120:pp 1961-1968.

Krishna M., Goel, Devendra K Gupta 2009. Huchisons Pediatrics. In: Krishna M Goel. Hematological disorders. first edition. Pheasant Run Drive, Missouri, U. S. A, pp (302).

Lagia, A., Eliopoulos, C., Manolis S. 2006. Thalassemia: macroscopic and radiological study of a case. *International J. of steoarchaeology*., Vol. 17 (3): pp 269-285.

Louis C. K. Low (2008). Growth of children with B-thalassemia major. Indian J. of Pediatrics, Vol. 72 (2): pp 156-164.

Margaret A., Hollar, DO. 2002. The hair on end sign 1. Radiology august vol.1 (224):609-610.

Mehri Ghafourian Boroujerdnia, Mohammad Ali Assareh Zadegan, Khoda Morad Zandian, Morteza Haghirizadeh Rodan 2009. Prevalence of Hepatitis – Cvirus (HCV) among Thalassemia patients in Khuzestan Province, South West Iran. *Pakistan. j. of medical sciences*. Vol. 25 (1), pp 113-117.

Neeraj Shah, Anupa Mishva, Dhaval Chauhay C Vova, N R Shal, 2010. Study on effectiveness of transfusion program in thalassemia major patients receiving multiple blood transfusion. *Asian J. Transfusion sciences*, Vol. 4 (2), PP. 94-98.

Orky Weizen – Sten, Konstantin Adamsky, Ninette Amariglio, Eliezer Rachmilewitz, Lanra Breda, Stefano Rirello, et al, 2006. mRNA expression of iron regulatory genes in B-Thalassemia intermediates and B thalassemia major. *American- J. of hematology* Vol. 81 (7) : pp 479 – 483.

Orzincolo C., Castaldi G., Bariani L., Scutellari PN. 1994. The evolutionary effects of therapy on skeletal lesions in B-thalassemia. *Radiol Med*., vol. 87(4): pp 381-388.

Pat Mahachoklertwahana, Vorachai Siriknlchayanonta, Ampaiwan. Chuanisamivt, Patcharre Karnsonbat, lulin Choubtum, Arpovn Sri phraprada, et al. 2003. Bone Histo morpho metry in Children and Adolescents with B-thalassemia disease Iron associated Focal osteomalacia. Journal of clinical endocrinology and metabolism vol.. 88 (8): pp 3966-3972.

Portincasa P. et al. 2004. Impaired gallbladder motility and delayed Orocecal transit contribute to pigment gallstone and biliary sludge formation in beta thalassemia major adults. *World J. Gastroenterol*. Vol. 10 (16). pp. 2383-2390.

Robert M., Kligman, Richard E,Behraman, Hal B. Jenson, Bonita F. Stanton, 2007. Nelson Text book of Pediatrics (18th ed). In: Michael R. DeBaun and Elliott Vichinsky. Hemoglobinopathies. Saunders Elsevier, Philadelphia, USA, PP. 2033-2035.

Roberto Maladonado, Richard G.Barr. 2000. Beta thalassemia (Coolys) anemia. *Applied Radiology Journal.,* Vol. 29, (1) p 1.

Salehi, MR., Farhud, DD., Tohidast, TZ., Sahebjamee M. 2007. Prevalence of Orofacial Complication in Iranian Patients with B- Thalassemia. *Iranian J. Publ Health*, Vol. 36(2): pp43-46.

Stanley L. Schrier, Emanuele Angelucci 2005. New Strategies in the Treatment of Thalassemia. *Annual Review of medicine*, Vol.56:pp 157-171.

Tunaci M., Tunaci A., Engin GO., Ozkorkmaz B., Dincol, G., Acunas G., Acunas B. 1999. Imaging features of thalassemia. *Eur. Radiol*. Vol. 9(9): pp 1804-9.

Udita Dewan, Niraj Kumari, Awadesh Jaiswal, Sarjay Behari, Manoj Jain, 2010. Extramedullary hematopoiesis with undiagnosed early myelofibrosis causing spastic compressive myelopathy: case report and review. *Indian J. Orthop*. Vol. 44(1): pp 98-103

****