Spinal cord compression and extramedullary haematopoiesis in Beta thalassemia patients

Thesis submitted for partial fulfillment of master degree in Pediatrics

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Abn:	abnormal
AIHA:	acquired immune hemolytic anemia
CT:	computed tomography
Dec:	decreased
DIC:	disseminated intravascular coagulation
EMH:	extramedullary hematopoiesis
G6PD:	glucose-6-phosphate dehydrogenase
GH:	growth hormone
Hb:	hemoglobin
HU:	hydroxy urea
Incr:	increased
MRI:	magnetic resonance imaging
PC:	protein C
PS:	protein S
N:	normal
RBCs:	red blood cells
SCC:	spinal cord compression
STD:	soft tissue density
Tc:	technicium
TI:	thalassemia intermedia
TM:	thalassemia major
Tr:	transfusion
TTP:	thrombocytopenic purura

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Hemolytic Anemias

Definition: Hemolysis is the premature destruction of erythrocytes, and it leads to hemolytic anemia when bone marrow activity cannot compensate for the erythrocyte loss.

Clinical presentation depends on whether the onset of hemolysis is gradual or abrupt and on the severity of erythrocyte destruction.

A patient with mild hemolysis may be asymptomatic. In more serious cases, the anemia can be life threatening, and patients can present with angina and cardiopulmonary decompensation *(Shick et al., 2005)*.

Skull and skeletal deformities can occur with a marked increase in hematopoiesis, expansion of bone in infancy, and early childhood disorders such as sickle cell anemia or thalassemia *(Glader, 1999)*.

Frequency: Internationally Hemolytic anemia represents approximately 5% of all anemias.

Mortality/Morbidity: The overall incidence of death is low. Morbidity is dependent on the etiology of hemolysis and the underlying disorder such as sickle cell anemia or malaria *(Konsu et al, 2004)*.

Clinical presentation: Tachycardia and dyspnea symptoms occur when the onset of hemolysis is abrupt and the anemia is severe.

Angina and heart failure symptoms can occur in patients with underlying cardiovascular disease and severe uncompensated hemolysis.

Hemosiderosis, leg ulcers, folate deficiency, and gallstones also can occur.

Jaundice may occur because of a modest increase in indirect bilirubin in hemolysis.

Splenomegaly occurs in hereditary spherocytosis and other hemolytic anemias but is not present in other hemolytic disorders such as G-6-PD deficiency *(Hamilton, 2004)*.

Causes: More than 200 causes for hemolysis exist, the main types include:

- Hereditary disorders include erythrocyte membrane and enzymatic defects and hemoglobin abnormalities. Some hereditary disorders include the following:
    - G-6-PD deficiency
    - Hereditary spherocytosis
    - Sickle cell anemia
- Acquired hemolytic conditions can be due to immune disorders, toxic chemicals and drugs, antiviral agents (e.g., ribavirin), physical damage, and infections. They can include the following:
    - AIHA
    - Microangiopathic anemia
- AIHA and hereditary spherocytosis are classified as examples of extravascular hemolysis because the RBCs are destroyed in the spleen and other reticuloendothelial organs.
- Intravascular hemolysis occurs in hemolytic anemia due to prosthetic cardiac valves, G-6-PD deficiency, TTP, DIC, and paroxysmal nocturnal hemoglobinuria (PNH) *(Shah, 2004)*.

Thalassemia

Historical back ground:

The first definitive descriptions of Thalassemia were published independently in the United States and Italy in 1925. In the United States, Cooley, a pediatrician from Detroit, identified a group of children of Mediterranean origin with profound anemia, enlargement of the spleen and peculiar bone changes *(Weatherall, 2004)*.

The unusual name by which the disease is known today was invented by Whipple when he was working as a pathologist in' Rochester in 1932.

Whipple decided on the name "thalassic anemia" – thalassa means sea in Greece - and then shortened it to thalassemia.

From early as the 1940s, it was clear that the term "thalassemia" is a geographical as well as a literary misnomer *(Weatherall et al, 2001)*.

Normal Human Hemoglobin

1. Function of Hemoglobin :

Hemoglobin is essential for the tissues to receive a constant supply of oxygen. *(Honig, 2004)*.

2. Genetics:

The genes for the globin chains occur in two clusters ε,δ,γ and β on chromosome 11 and ζ and α on chromosome 16. Two types of γ chain, G γ and A γ occur depending on whether there is a glycine or alanine aminoacid at position 136 in the polypeptide chain. The α chain gene is duplicated and both α genes (α_1 and α_2) on each chromosome are active *(Hoffbrand et al, 2001)*.

3. Ontogency of human Hb = development express of Hb:

Within the RBCs of an embryo, fetus, child and adult, six different hemoglobins may normally be detected the embryonic hemoglobin, Gower-1, Gower-2, and Portland, the fetal hemoglobin; Hb F and the adult hemoglobins; Hb A and A_2. The electrophoretic imobilities of hemoglobins vary with their chemical structures *(Nelson, 2004)*.

a. Embryonic Hemoglobins:

The blood of early human embryos contains two slowly migrating hemoglobins, Gower-1 and Gower-2, and Hb portland, which has HbF-like mobility. Hb Gower-1 has the structure ζ_2 , ε_2 and gower-2, α_2, ε_2. Hb Portland has the structure ζ_2, γ_2. In embryos of 4-8 weeks gestation, the gower hemoglobins predominate, but by the 3rd month they have disappeared *(Nelson, 2004a)*.

b. Fetal Hb :

HbF contains y polypeptide chains in place of the β- chains of HbA. After the 8th gestational week, HbF is the predominant hemoglobin. During the 3rd trimester, a gradual decline occurs, so decreases rapidly postnatally, and by 6-12 months of age only a trace is present *(Nelson, 2004)*.

c. Adult Hb :

Some Hb A ($\alpha_2\beta_2$) can be detected in even the smallest embryos. Accordingly, it is possible as early as 16-20 weeks gestation to make a prenatal diagnosis of major β-chain hemoglobinopathies, such as thalassemia major *(Nelson, 2004)*.

Embryonic	Gower 1	ζ_2 ε_2
	Gower 2	α_2 ε_2
	Gower 3	ζ_2 γ_2
Fetal	Hemoglobin F	α_2 γ_2
Adult	Hemoglobin A1	α_2 β_2
	Hemoglobin A2	α_2 δ_2

Tab. (1): The composition of embryonic, fetal, and adult Hb. *(Nelson, 2004)*

Thalassemia syndromes:

The thalassemias are the most common genetic disorder on a world wide basis. The selective pressures that have made the thalassemia so common are not known. Before the genetic basis for the disorder was appreciated, the thalassemias were classified on the basis of clinical severity *(Cohen, 2004)*.

Patients with major clinical manifestations and severe anemia were said to have thalassemia major, whereas those whose anemia was not so severe as to necessitate regular transfusions were said to have thalassemia intermedia. After the hereditary character of thalassemia was appreciated, parents of children with thalassemia major were found to have little or no anemia, despite morphologically abnormal erythrocytes. They were said to have thalassemia minor *(Brodie,2005)*.

Children with thalassemia have a shorter red cell life, fetal hemoglobin in their red cells until an older age than normal, and red cells that are more sensitive to oxidative stress *(Weatherall et al., 2001)*.

PREVALENCE AND GEOGRAPHIC DISTRIBUTION

Thalassemia is considered the most common genetic disorder worldwide. It occurs in a particularly high frequency in a broad belt extending from the Mediterranean basin through the Middle East, Indian subcontinent, Burma, and Southeast Asia.

The highest concentration of the α thalassemia genes is found in Southeast Asia and among those populations who have their origin along the west coast of Africa.

In the eastern oases of Saudi Arabia, more than 50% of the population appears to have a clinically silent form of α thalassemia *(Aliberti et al.,2001)*.

About 3% of the world's population (150 million people) carry β thalassemia genes. These genes are particularly prevalent in inhabitants of Italy and Greece. The highest prevalence of the carrier state in descending order has been found in Sardinia, the delta region of the Po River near Ferrara and Sicily *(Nelson, 2004)*.

In Greece, the prevalence varies considerably, ranging from less than 5% to nearly 15% in the southern and central areas, as it also is in Cyprus. In Sardinia the incidence of homozygous β thalassemia is 1:250 live births. There are an estimated 3500 individuals with thalassemia major in Greece *(Giardina, 2001)*.

Migration, changing marriage patterns among ethnic groups, and differences in the relative growth of populations can be expected to change the distribution and prevalence of thalassemia. The distribution of the thalassemias in the Old World and in Melanesia is similar to that of malaria, suggesting that a state of balanced polymorphism permitted the persistence of a potentially lethal gene. This hypothesis is

supported by the demonstration of an increasing frequency of β thalassemia trait with increasing age in Northern Liberia and Sicily*(Giardina, 2001)*.

The purported advantage afforded the thalassemic red cell has been attributed to its low concentration of hemoglobin, an essential nutrient for the malaria parasite. In addition, both Hb F and Hb H appear to inhibit the growth of the parasite *(Sinis et al., 1996)*.

Age of Presentation:

Patients with severe β-thalassemia are usually diagnosed between 6 months and 2 years of age when the normal physiologic anemia of the newborn fails to improve. Occasionally, the disease is not recognized until the child is 3 to 5 years of age because the infant is able to partially compensate for the marrow's inability to produce hemoglobin A by prolonged production of Hb F. On presentation affected infants usually have pallor, poor growth and development, and abdominal enlargement *(Olivieri,1999)*.

Classification of Thalassemias :

Type of thalassemia	Globin genotype	Hematologic features	Clinical expression	Hemoglobin findings
β-thalassemia β-homozygous	β -/ β -	Severe anemia Normoblastemia	Cooley's anemia	HBF>90% No HbA,HbA2
β+homozygous	β +/ β +	Anisocytosis, moderately severe anemia	Thalassemia intermedia	HbA,20%-40% HbF 60%-80%
β heterozygous	β / β -	Microcytosis, hypochromia, mild to moderate anemia	May have splenomegaly, jaundice.	increased HbA2 and HbF
β heterozygos	β / β +	Microcytosis hypochromia, mild anemia	Normal	Increased HbA2 and HbF
β-silent carrier, heterozygous	β / β +	Normal	Normal	Normal
δβ-heterozygous	δ β /(δ β)-	Microcytosis, hypochromia, mild anemia	Usually normal	HbF 5%-20%, HbA2 normal or low
γδβ heterozygos	γδβ/(γδβ)-	Newborn : microcytosis, hemolytic anemia, normoblastemia Adult: similar to heterozygous δβ	Newborn : hemolytic disease with splenomegaly Adult: similar to heterozygous δβ	Normal
α-thalassemia α -silent carrier α - trait	-α/ α , α α, α/ α. α -, α/-, α -,-/ α, α	Mild microcytosis or normal microcytosis hypochromia, mild anemia	Normal Usually normal	Newborn :Hb Bart's5%-10%. Child or adult: normal
HbH disease	-, α /-,-	microcytosis, inclusion bodies by supravital staining,moderately severe anemia	Thalassemia intermedia	Newborn :Hb Bart's20%-30% Child or adult: HbH 4%-20%
α- hydrops fetalis	-,-/-,-	anisocvtosis, poikilocytosis, severe anemia	Hydrops fetalis: Usually stillborn or neonatal death	Hb Bart's(γ4) 80%-90%, no HbA or HbF

Tab. (2) : Clinical and hematological features of the principle forms of thalassemias.*(Nelson, 2004)*

Molecular pathology of thalassemia :

The development of techniques for gene cloning, DNA sequencing and assessment of gene function have been exploited to define molecular pathology of the thalassemias in remarkable detail.

Most of the α thalassemia syndromes result from gene deletions. The α-globin genes appear to be predisposed to deletions because of tandemly duplicated sequences in the α-gene cluster. In contrast, most of the β thalassemia syndromes result from one or more nucleotide substitutions or deletions in genes that are otherwise intact. The well-known clinical heterogenicity of the thalassemia syndromes is a reflection of the great heterogenicity of mutations affecting the globin genes *(Chan et al., 2002)*.

α Thalassemia

Two α thalassemia phenotypes are recognized; one is characterized by thalassemia minor in the heterozygous state and the other is marked by no clinical or hematologic abnormality in the heterozygous state. The former phenotype has been referred to as α thalassemia 1 and the latter has been labeled α thalassemia 2*(Lam et al., 1999)*.

It is now recognized that the α thalassemia 1 determinants are associated with complete absence and the α thalassemia 2 phenotypes with only a reduction in α–globin syntheses. Accordingly, these two major α thalassemia variants are now designated α° thalassemia and α^{+} thalassemia. The α° thalassemias result from deletions that involve both α-globin genes *(Leung et al., 2002)*.

Some of the α^{+} thalassemias result from deletions involving only one of the two α-globin genes (-α) and others from non deletion mutations that limit α -gene expression.

Interactions of the mutations causing deficient α-globin synthesis produce a spectrum of phenotypes that can be grouped into four clinical syndromes. In each syndrome, the severity of symptoms correlates closely with the deficiency of α-globin chains relative to β-chains *(Weatherall et al.,2001)*.

Tab. (3): Clinical and hematological features of the α thalassemia syndromes *(Nelson, 2004)*.

phenotype	**genotype**	**Clinical features**	**Hemoglobin variants**	
			neoborn	**After first year**
Hydrops fetalis	(--/--)	Fetal or neonatal death with severe anemia	Hb Bart's(80-90%) Hb H, Hb Portland	_____
Hemoglobin H disease	(--/-α) (--/αα^{T}) CS (--/α α) (αα^{T}/ αα^{T})	Chronic hemolytic anemia (thalassemia intermedia)	Hb Bart's(20-40%)	Hb H (5-40%) ±Hb Bart's ±Hb CS
Thalassemia minor	(--/αα) (-α/-α) (-α/ αα^{T})	Little or no anemia, decreased MCV, MCH	Hb Bart's(2-10%)	None
Silent carrier	(-α/αα)	No clinical or hematological abnormality	Hb Bart's(0-2%)	None

β THALASSEMIA

The β thalassemias, like the α thalassemias, result from mutations that cause diminished production of mRNA and decreased synthesis of structurally normal globin. In contrast to α thalassemias, most of the β thalassemia syndromes are caused by mutations affecting gene regulation or expression rather than gene deletion *(Olivieri et al., 2001)*.

Study of globin chain synthesis in the homozygous state reveals two major types of β thalassemia, one with some residual β chains (β^+ type) and another with no β chains (β° type). In individuals with β^+ thalassemia, the amount of β- globin mRNA in reticulocytes and bone marrow normoblasts is decreased three- to tenfold *(Olivieri et al., 2001)*.

Over 200 mutations have been described in thalassemia phenotype. About 20 mutations account for the vast majority of affected patients and constitute 80% of the known thalassemia world wide *(Honig, 2004)*.

It have been determined that five or six mutations usually account for more than 90% of the cases of β-thalassemia, which are IVS-I nt 110, IVS-I nt 6, IVS-I nt l, IVS- II nt 745, IVS-II nt l and codon 39. It has been found that IVS-I nt 110 is the most common mutation followed by IVS-I nt 1 followed by IVS-I nt 6 *(Kazazian 1990)*.

The patients having these common mutations receive more frequent blood transfusions than the rest of the patients particularly those having the mutation IVS-I nt 110. This last group also manifests significant reduction in weight. Patients having the mutations IVS-I nt 6 and or IVS-I nt 1 receive the least frequent blood transfusion and none of them had weight below the 5th percentile *(Khalifa et al,1995)*.

Example of Mutation :

i. Promoter region mutation = transcription mutation.
ii. Chain terminator mutation which either non-sense or frame shift.
iii. Splicing mutation (SPL).
iv. Capping/polyadenylation mutation *(Wintrob, 1999)*.

In β^{+} Thalassemia :

β-Globin mRNA is markedly reduced resulting in decrease in β-globin synthesis.

In β° Thalassemia :

There is total absence of β-globin mRNA synthesis. If both parents are carriers, 1 out of 4 of their children may be thalassemic. Mass screening for thalassemia carriers is needed in areas of high prevalence *(Olivieri et al., 1999)*.

Pathophysiology:

Selective deficiency of one or more polypeptide chains has two immediate consequences; decreased hemoglobin synthesis and imbalance between alpha and non alpha chain production. The former is a major determinant of red cell hypochromia and is responsible for erythrocytosis in heterozygotes, but it is of little clinical significance *(Atweh et al., 2003)*.

For more devastating is the biosynthetic disruption of globin balance in the absence of complementary globin chains with which to bind, chains whose synthesis is normal form aggregates, precipitate, and lead to premature cell destruction *(Bernard et al., 1993)*.

Tab. (4): Clinical and hematological features of the β thalassemia syndromes.*(Taher et al., 2006)*

	Major	Intermedia	Minor	Minimal
Severity of manifestations	++++	++	+,±	±,0
Genetics	homozygotes, double heterozygotes	homozygotes, double heterozygotes, rarely heterozygotes	heteroz-ygotes	heteroz-ygotes
Splenomegaly	++++	++,+++	+,0	0
Jaundice	+++	++,+	0	0
Skeletal changes	++++,++	+,0	+,0	0
Anemia	<7 gm/dl	7-10 gm/dl	>10gm/ dl	normal
Hypochromia	++++	+++	++	+
Microcytosis	+++	++	+	0
Target cells	10-35%	++	+	±
Basophilic stippling	++	+	+	0,+
Reticulocytes	5-15%	3-10%	2-5%	1-2%
Nucleated red cells	+++	+,0	0	0

Clinical and hematological features of β thalassemia major

1. Type of anemia:

Hypochromic microcytic anemia becomes apparent 3-6 months after birth when the switch from gamma to beta chain production takes place *(Nelson, 2004)*.

The course of the disease in childhood depends almost entirely on whether or not the child is maintained on an adequate transfusion program. If transfusions are possible, the affected children grow and develop almost normally. The disease only presents a problem when the effects of iron loading resulting from ineffective erythropoiesis and from repeated blood transfusions become apparent at the end of the first decade *(Weatherall et al., 2001)*.

2. Skeletal changes:

Bony disease in β-thalassemia is related to erythroid expansion.

The most striking skeletal changes are seen in the skull and facial bones. There is bossing of the skull and overgrowth of the maxillary region, the whole face gradually assumes a mongloid appearance *(Honig, 2000)*.

Bone marrow expansion can lead to a variety of other distressing symptoms, particularly pathological fractures, poor dentition and attacks of recurrent sinusitis due to inadequate drainage, marked osteoporosis and cortical thinning are noticed in thalassemic patients. It is more common in the lumbar vertebrae and femoral necks *(Chan et al., 2002)*.

Recently there has been considerable interest in the possibility that there may be subsets of individuals who are genetically susceptible to developing osteoporosis *(Jensen et al, 1998)*.

3. Infection :

It was suggested that the incidence of infection in early child hood had been markedly reduced in children maintained on an adequate hemoglobin level. In recent years, although there is still an awareness of the dangers of infection, particularly after splenectomy, there has been a major change in emphasis toward concerns about blood-borne infection, notably hepatitis B and C. and human immunodeficiency virus (HIV) *(Wonke et al, 1998)*.

Patterns of Infection with Changing Management:

In an extensive retrospective study of the patterns of infection in thalassemic children maintained at different hemoglobin levels, *Modell and Berdoukas (1984)* concluded that the most serious infections were pneumonia, pericarditis, the sequelae of streptococcal infections, meningitis, peritonitis, and osteomyelitis.

Further analysis suggested that pneumonia and septicemia were significantly associated with splenectomy and a low transfusion regimen, and that in patients who had been maintained at a satisfactory hemoglobin level these infections had almost disappeared *(Atkinson et al., 1996)*.

They also observed that other serious infections including meningitis, peritonitis, and osteomyelitis are only seen in splenectomized patients and that they have no obvious relationship to anemia. Finally, they noted that pericarditis is

also unrelated to anemia and splenectomy but is very clearly related to age, occurring in childhood or later. They suggested that this may reflect a relationship between iron overload and pericarditis.

In any child who has had the spleen removed early in life the most important organisms are Streptococcus pneumonia, Hemophihis influenza, and Neisseria meningitis *(Alter, 2002)*.

The widespread use of prophylactic penicillin and appropriate immunization after splenectomy has undoubtedly reduced the frequency of severe infections in splenectomized thalassemic children *(Steinberg et al.,2001)*.

Organisms That Attack Iron-Loaded Patients:

The only pathogens that have been shown quite unequivocally to occur with an increased frequency in iron load patients are those of the Yersinia genus, which normally have a low pathogenicity and an unusually high requirements for iron. They only become pathogenic in the presence of iron bound to desferrioxamine.

These infections are usually characterized by severe abdominal pain, diarrhea, vomiting, fever, and sore throat. They may also be associated, on occasion, with rupture of the bowel *(Manconi et al., 1998)*.

Hepatitis B Virus (HBV):

It is estimated that about 350 million people worldwide are persistent carriers of hepatitis B. The virus persists in about 10 percent of infected immunocompetent adults.

Because HBV is primarily a blood-borne infection, transfusion-dependent thalassemic children are at particular risk,

depending on its prevalence in their community and the effectiveness of donor screening programs *(Zemel et al, 1998)*.

Hepatitis C virus (HCV) :

Following the identification of HCV it soon became clear that this infection is wide spread and presents a serious risk to patients with transfusion dependent thalassemia *(Wonke et al, 1998)*.

Human immunodeficiency virus (HIV):

The human immunodeficiency viruses HIV-1, HIV-2 belong to the lentivirus subfamily of retro viruses. They can both give rise to the acquired immunodeficiency syndrome (AIDS).

Since these viruses can be transmitted by blood transfusion or perinataly it is clear that thalassemic patients form a high risk subgroup in any population in which this infection is common *(Manconi et al,1998)*.

Malaria:

The disease has returned to many countries from which it seemed to have disappeared and, even more frighteningly, drug resistance is now widespread.

Children with severe forms of thalassemia are subject to attacks of acute malaria like any other child; the protective effect of thalassemia against malaria is relative; no form of thalassemia protects any individual completely against the infection. Chronic malaria, as well as exacerbating the anemia of thalassemia, may also increase the degree of splenomegaly *(Wambua et al., 2006)*.

Thalassemic children are particularly at risk from blood-borne malaria. Therefore, in any thalassemic child in a malarious area who presents with fever, drowsiness progressing to coma, renal failure, hemoglobinuria, hypoglycemia, or simply a rapidly worsening anemia, a diagnosis of malaria must be considered, regardless of the number of parasites in the peripheral blood *(Weatherall et al, 2000)*.

4. Liver Disease:

In young adults with thalassemia major liver disease remains a common cause of morbidity and mortality. Although it has been realized for many years that iron overload, acquired through transfusion and increased gastrointestinal absorption, is a major factor in the generation of liver disease, more recently, with the increasing recognition of blood-related viral hepatitis, it has become clear that the pathogenesis of liver damage is extremely complex *(Steinberg et al.,2001)*.

Mechanism of Liver Damage:

Iron produces cellular injury with progression to fibrosis and cirrhosis. This may be mediated in several ways. It promotes free-radical mediated lipid peroxidation and mitochondrial dysfunction *(Hershko et al., 1998)*. The deposition of hemosiderin in lysosomes may lead to fragility and subsequent rupture of their membranes.

Furthermore, iron overload may potentiate further iron loading; up regulation of the transport of non-transferrin-bound iron has been observed in cultured hepatocytes (Konologhiorghes *et al., 2003)*.

Blood-borne viral infection is another major factor in the high frequency of liver disease in thalassemic patients, and iron may potentiate the effects of viral hepatitis. Hepatic biopsy provides definitive information with respect to quantitative body iron stores.

Age, the iron content of the liver, associated hepatitis and the possibly splenectomy may all play a roll in determining the time at which liver disease is established *(Parti et al, 1998).*

5. Splenomegaly:

The constant exposure of the spleen to red cells with inclusions consisting of precipitated globin chains gives rise to the phenomenon of "work hypertrophy" progressive splenomegaly occurs in both α and β Thalassemia and may exacerbate the anemia *(Weatherall et al., 2001).*

6. Endocrine disorders :

Endocrine dysfunction is well recognized in transfusion dependent thalassemic patients and is thought to reflect the consequence of iron overload. The ability of desferrioxamine to prevent endocrine damage is less clear *(Cappellini et al, 2000).*

a) Growth and development:

The most common endocrinal problem is delayed growth. The etiology of impaired growth includes the decreased synthesis of insulin like growth factor-I (IGF-1) which might be secondary to disturbed growth hormone insulin like growth factor-I (GH-IGF-1).

Growth retardation is less in well chelated patients. Impaired growth hormone production has been reported in some patients. Failure of adrenal and androgen production may also contribute to growth failure. Thyroid deficiency is an additional potential contributing factor *(Roth et al, 1997).*

In Egypt, *Ishak* et al. (1990) proved that bone age retardation was positively correlated with total amount of blood transfused ,

which suggests that iron over load may have an etiology of growth retardation in thalassemia.

b) <u>Puberty:</u>

It will occur normally in about third of patients with thalassemia. Breast development in females tends to begin normally but menarche is frequently delayed until late teenage. Eventually, many female patients who progress through puberty normally will develop secondary amenorrhea due to progressive iron accumulation *(Nathan et al., 199٨)*.

Delayed puberty and hypogonadism

This is the second most common problem, and is thought to be a result of iron overload which leads to damage at pituitary, hypothalamic or gonadal level *(Low, 1997*).

Males tend to have low base line testosterone levels *(Ishak et al., 1990)*. They have immature, sparse facial and body hair, with lack of secondary sexual characteristics *(Chrysis et al., 2001)*.

Hypogonadotropic hypogonadism is the commonest and most frequent endocrine dysfunction in β-thalassemia *(Raiola et al., 2003)*.

Ishak et al. (1990) mentioned that delayed sexual maturation was evident in 75% of male and 66.4% of female Egyptian thalassemic patients above 11 years.

c) <u>Hypothyrodism:</u>

Thyroid deficiency is an additional contributing factor. However, *Ishak et al. (1990)* proved that most of Egyptian patients had normal T4 level. This indicates that thyroid

dysfunction is not a major contributing factor of retarded growth in Egyptian thalassemic patients.

d) Diabetes Mellitus:

It is a well documented complication of thalassemia major particularly among polytransfused patients. Iron deposition in the liver may produce insulin resistance by interfering with the ability of insulin to suppress hepatic glucose production. It was found that the incidence of DM was lower in those receiving good chelation *(Low, 2001)*.

e) Adrenal:

Iron deposition is limited primarily to the zona glomerulosa *(Low, 2001)*, the site of mineralocorticoid production.

7. Renal :

Kidneys are enlarged due to extramedullary haematopoiesis. Dark brown urine may be present reflecting a severe degree of ineffective erythropoiesis, because it is due to excretion of products of heme catabolism *(Tantawi et al, 2001)*.

8. Thrombo-embolic complication:

A higher than normal incidence of thromboembolic events has been observed in adult patients with beta thalassemia major and certain haemostatic anomalies found in these patients suggest the existence of a chronic hypercoagulable state *(Eldor et al., 1999)*.

Significantly elevated plasma levels of thrombin-antithrombin III complexes were observed to the same extent in thalassemic children and adults. The level of factor II was decreased while factors V, VII, X and plasminogen were within the normal ranges *(Eldor et al., 1999)*.

There is decreased level of protein-C and protein-S in the circulation with appearance of markers for endothelial cell activation *(Akar et al., 2000)*.

9. Neuromuscular abnormalities:

Neuromuscular complications of thalassemia are not common. Walking was delayed beyond 18 months in about one-third of the patients on moderate transfusion regimen, while speech and intellectual development appeared to proceed normally. 20% of patients had histories of episodes suggesting cerebral ischemia, with focal neurological episodes.

Neurosensory deafness has been noted with improvement in hearing after commencement of regular blood transfusion and it was relatively common in inadequately transfused young thalassemics *(Chrysis et al., 2001)*.

There is no doubt that severe cranial deformities resulting from massive expansion of the bone marrow can result in symptoms of this kind, or involvement of the optic nerve, but these complications are only seen in patients who have been maintained at extremely low hemoglobin levels *(Wonke, 1998)*.

10. Intelligence and behavioural patterns:

The mental status of patients of thalassemia major were evaluated, intelligence testing revealed no difference from normal children of the same age and social group in well transfused patients.

But abnormalities of behaviour and character in the form of depression and anxiety were noted *(Brodie., 2005)*.

β THALASSEMIA INTERMEDIA

It has been apparent since the earliest descriptions of thalassemia that there are forms characterized by moderate anemia, jaundice, and splenomegaly that, although not as severe as the transfusion-dependent varieties are clearly worse than the carrier states *(Ho et al., 1998)*.

Definition:

There is no adequate definition of β thalassemia intermedia, any thalassemic patient with a haemoglobin level persistently below 9 to 10 g/dL, particularly if there is associated splenomegaly, falls into the intermediate class of β thalassemias.

Clearly, the term thalassemia intermedia can cover a broad and shifting clinical spectrum, from almost complete health to a condition characterized by severe growth retardation and skeletal deformity that requires transfusion therapy; it is a diagnosis that can be made only after a considerable period of observation and that often requires revision *(Taher, 2006)*.

Tab. (5): Genetic interaction that result in the phenotype of β thalassemia intermedia *(Wainscoat et al.,1987)*.

1. Mild deficit in β globin chain production
   - Homozygous mild β+ thalassemia
   - Compound heterozygosity for severe β° or β+ and mild β+ thalassemia
   - Interactions of β° with 'silent' β thalassemia,
   - Homozvgosity for 'silent' β thalassemia
2. Reduced globin chain imbalance due to co-inheritance of α and β thalassemia
   - Homozygous or compound heterozygous thalassemia with 2 or 3 α gene deletions
   - Homozygous or compound heterozygous severe β° or β+ thalassemia with non-deletion α2 gene mutation
   - Homozygous or compound heterozygous severe β+ thalassemia with 1 or 2 α gene deletions
3. Severe β thalassemia with increased capacity for γ chain synthesis
   - Homozygous or compound heterozygous β° or β+ thalassemia with heterocellular HPFH
   - Homozygous or compound heterozygous β° or β+ thalassemia with particular β globin RFLP haplotype
   - Mechanism unknown
4. Deletion forms of δβ thalassemia and HPFH
   - Homozygous (δβ)° or (A γδβ)° thalassemia
   - Compound heterozygosity for β° or β+ and (δβ)° or (A γδβ)° thalassemia
   - Homozygosity for Hb Lepore (some cases)
   - Compound heterozygosity for Hb Lepore and β° or β+ thalassemia (some forms)
   - Compound heterozygosity for (δβ)°, Gγβ+ or Aγβ+ HPFH and β° or β+ thalassemia
   - Compound heterozygosity for (δβ)° thalassemia and (δβ)° HPFH
5. Compound heterozygosity for β or δβ thalassemia and β chain structural variants
   - Hb S, C, E/β or δβ thalassemia
   - Many other rare interactions
6. Other β thalassemia alleles or interactions
   - Dominant β thalassemia
   - β thalassemia trait associated with ααα or αααα globin gene duplications
   - Highly unstable β globin chain variants

Unusual Efficiency of HbF Production in Generating β Thalassemia Intermedia:

It has long been realized that variation in the ability to produce HbF in the postnatal period must be a major factor in the generation of the phenotype of thalassemia intermedia.

While many threads of evidence have pointed in this direction, some of the most convincing were early reports of individuals apparently homozygous for β° thalassemia who ran relatively mild clinical courses. In the families of some of these patients a determinant for heterocellular hereditary persistence of fetal hemoglobin (HPFH) appeared to be segregating *(Rees et al., 1999).*

Clinical Features

One of the hallmarks of β thalassemia intermedia is its late presentation compared with transfusion-dependent forms of the disease. Although there is considerable individual variation, overall it is usual for transfusion-dependent patients to come to medical attention in the first year of life, whereas those with thalassemia intermedia tend to present during second year or later.

Clinical manifestations are extremely variable. In some cases the disorder presents early in life with relatively severe anemia, while in others it may not appear until later due to a complication such as hypersplenism *(Steinberg et al., 2001).*

Many patients have been found to have this condition on routine clinical examination. Growth and development may be normal or there may be a similar pattern of retardation as occurs in under-treated transfusion-dependent β thalassemia. The most common symptoms are those of anemia and mild jaundice.

There is always some degree of splenomegaly. Bone changes are variable and range from none at all to the severe skeletal deformities characteristic of transfusion-dependent β thalassemia *(Taher, 2006)*.

Complications

Hypersplenism: Increasing splenomegaly leading to hypersplenism is a relatively common feature of β thalassemia intermedia. A proportion of the patients have to undergo splenectomy for worsening of their anemia, thrombocytopenia, or neutropenia *(Camaschella et al., 1995)*.

Iron loading: There is increasing evidence that although the rate of iron loading is much slower than in transfusion-dependent β thalassemia, patients with thalassemia intermedia do iron load and this may become of clinical importance in adult life.

Iron over load in β thalassemia intermedia is due to :

a) Ineffective erythropoiesis.
b) Peripheral RBCs break down *(Taher, 2006)*.

Endocrine function: Endocrine function is often maintained up to and beyond puberty. It appears that by the time these patients reach the third or fourth decades there is a significant incidence of diabetes mellitus, and other endocrine deficiencies *(Jensen et al., 1997)*.

Cardiac Function: Because of the slower rate of iron loading in β thalassemia intermedia than in transfusion-dependent forms of the disease it would be expected that, if cardiac complications occur at all, they would only be manifest in adult life *(Anderson et al., 2001)*.

Gallstones: Probably as a result of both ineffective erythropoiesis and hemolysis there is a high frequency of pigment stones *(Goldfarb et al., 1990)*.

Skeletal Deformities and Bone and Joint Disease: some patients with β thalassemia intermedia develop severe skeletal deformities, similar in every way to those seen in the under treated transfusion-dependent forms of the disease.

Pathologic fractures are also a major feature, particularly in older patients. There is also a particularly distressing complication involving the bones and joints that has been called "thalassemic osteoarthropathy" . This takes the form of a curious periarticular disease characterized by dull aching pains in the ankles, exacerbated by weight-bearing and relieved by rest *(Chan et al., 2000)*.

Radiologic changes include widening of the medullary spaces, thin cortices with coarse trabeculations, and evidence of microfractures in the region of the joints. Histologic analysis confirmes the presence of the latter and, in addition, shows osteomalacia and increased osteoblastic surface areas with iron deposition in the calcification front and cement lines. Acetabular protrusion has also been reported in patients with severe bone involvement *(Vichinisky et al., 1998)*.

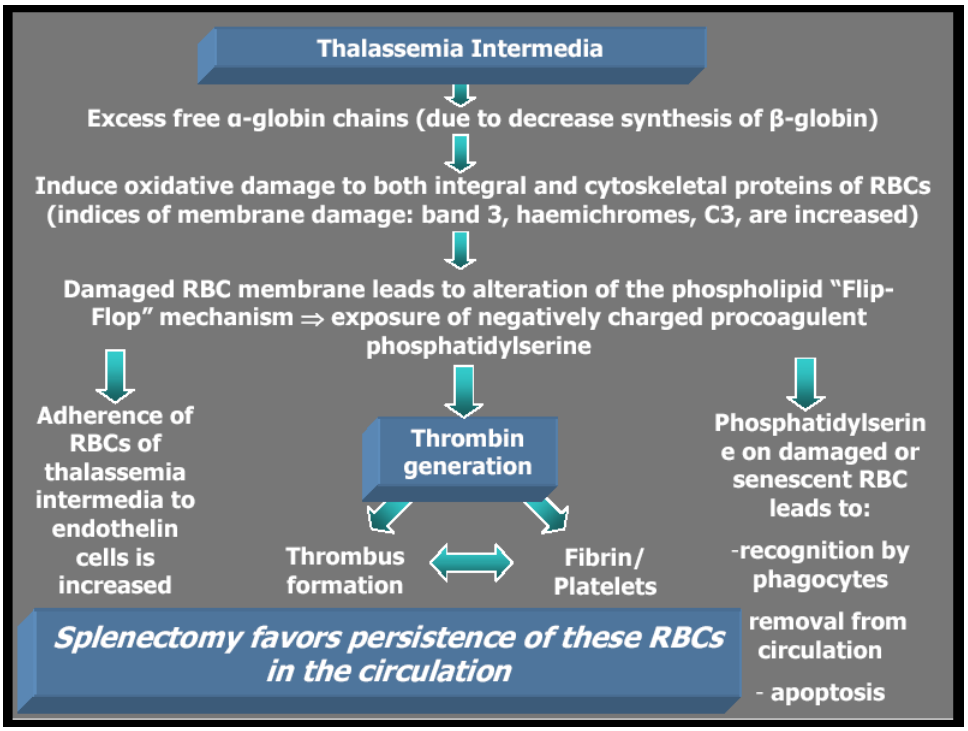
Extramedullary erythropoiesis: The generation of tumour masses composed of extramedullary erythropoeitic tissue is a frequent complication *(Aliberti et al., 2001)*.

The most common site is in the paraspinal region. Although they don't usually cause symptoms, there have been well documented case reports of spinal cord compression *(Alam et al., 1997)*.

Infection: The pattern of infection is similar to that outlined for transfusion-dependent β thalassemia.

Leg Ulcers: This is a relatively common complication of β thalassemia intermedia *(Weatherall et al., 2000)*.

Thromboembolic disease: There have been occasional reports of severe thromboembolic disease following splenectomy but it is not possible to assess the overall risk of thrombotic disease, nor is it clear whether it is related to the occurrence of recurrent priapism following splenectomy in patients with this type of thalassemia *(Barker, 1999)*.



This diagram shows factors favouring thrombosis in thalassemia intermedia *(Taher, 2006)*.

Laboratory features of Thalassemia

A. Hematological findings :

At birth there is no anaemia but the haemoglobin level decreases progressively during the first months of life in thalassemia major and after about three years of life in thalassemia intermedia.

The anaemia is typically hypochromic microcytic with a low mean cell haemoglobin (MCH) and mean cell volume (MCV).

The peripheral blood film shows marked anisocytosis and poikilocytosis, with many misshapen microcytes, occasional macrocytes and variable number of target cells. Erythroblasts are always present and may reach extremely high levels after splenectomy.

White cells and platelet counts are usually normal except when there is hyper splenism.

Ragged inclusion bodies can be seen in the cytoplasm of both nucleated and non nucleated red cells after incubation with methyl violate in a splenectomized patient.

The absolute reticulocyte count is rarely high although it tends to increase after splenectomy *(Kohean et al. 2004)*.

The bone marrow shows marked erythroid hyperplasia with a reversal of the myeloid erythroid ratio. The marrow also shows intense phagocytic activity with the presence of large foamy cells resembling Gaucher cells *(Alter, 2002)*.

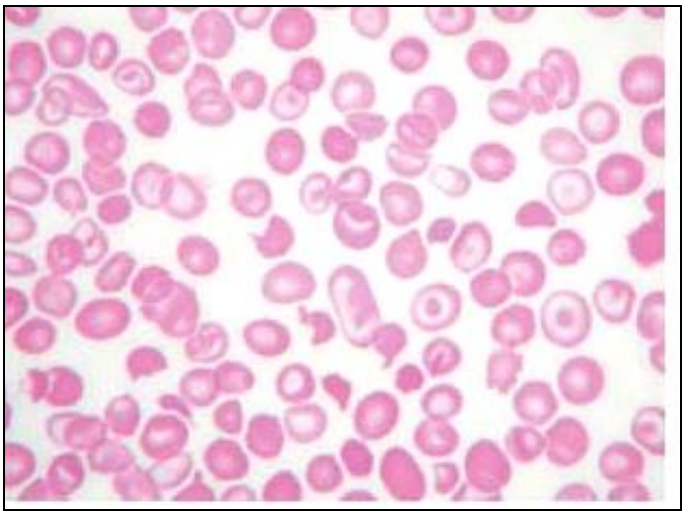


Fig. (1): Peripheral blood film in β thalassemia major showing hypochromia, anisocytosis, poikilocytosis and target cells.

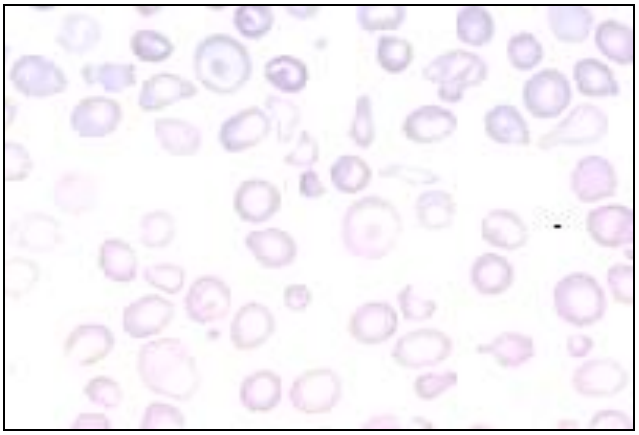


Fig. (2): Peripheral blood film in β thalassemia intermedia *(www.emedicine.com)*.

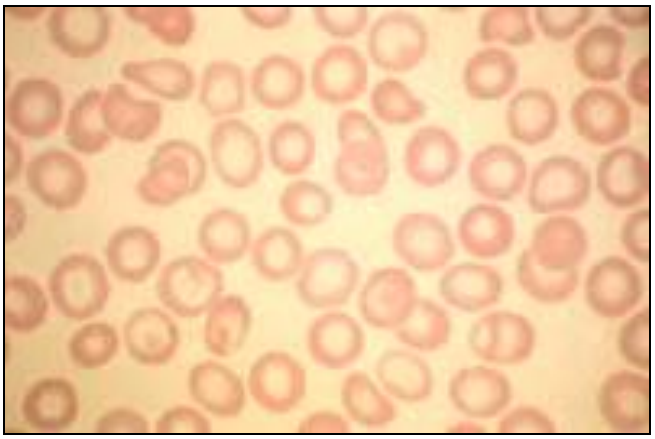


Fig. (3): Peripheral blood film in β thalassemia minor *(www.emedicine.com).*

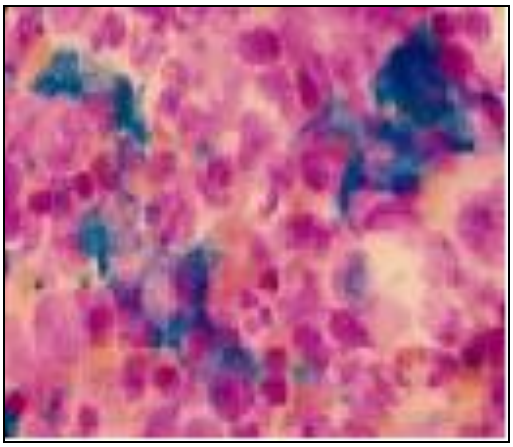


Fig (4): Excess iron in a bone marrow preparation *(www.emedicine.com).*

B. Biochemical changes :

1) Serum iron and ferritin :

Serum iron is elevated in children with severe β thalassemia, and in older patients the iron-binding capacity is fully saturated. The serum of such patients contains 2 to 7 µmol/L of non-specifically bound iron that is dializable and can be bound by transferrin from normal sera *(Fischer et al., 1999)*.

The measurement of plasma or serum ferritin is the most commonly used estimate of body iron stores in thalassemia. However, it has serious limitations, particularly in severely iron-loaded patients. The wide fluctuations that may occur at high ferritin levels may reflect a variety of mechanisms that alter the concentration independently of body iron load. These include ascorbate deficiency, acute and chronic infection, liver damage, hemolysis, and ineffective erythropoiesis.

The hepatic iron concentration remains the most effective guide to assessing body iron stores *(Brittenham, 2000)*.

2) Liver functions :

The serum is icteric with elevated unconjugated bilirubin ranging between 2-4 mg/dL. Liver function tests are frequently increased due to hepatic damage secondary to hemosiderosis *(Oliveri et al., 1999)*.

3) Other biochemical changes :

Serum zinc, serum ascorbic acid, vitamin E and folic acid are decreased. LDH is elevated as a consequence of ineffective erythropoiesis *(Steinberg et al., 2001)*.

C. Haemoglobin electrophoresis :

The hemoglobin of thalassemic patients is predominantly HbF. It tends to decrease with age, but it is always higher than normal, ranging from 10 to 90. The HbA2:HbAl ratio, which normally is about 1:30 is increased to less than 1:20 in thalassemia trait but HbA2 level in thalassemia major are variable *(Brodie., 2005)*.

D. Immunological changes :

The immunological studies revealed elevation of the mean level of immunoglobulins IgG, IgA and IgM in the non-splenectomized patients. After splenectomy, the mean level of immunoglobulin IgG and IgA were still elevated and IgM is depressed *(Abu El Hassan et al., 1993)*.

Radiological findings

Bony disease is related to erythroid expansion and not to iron overload or abnormalities in vitamin D metabolism. Maintenance of near normal hemoglobin levels result in suppression of erythropoesis and prevents, or partially reverses bony abnormalities. Radiological abnormalities may be present during the first 6 months of life but are usually not marked until about 1 year of age *(Jensen et al., 1998).*

Expansion of marrow cavities and thinning of cortices produce a variety of bony abnormalities in patients who are not optimally transfused accordingly, they become extremely fragile and prone to pathologic fractures.

The earliest changes appear in the hands and feet, where expanding marrow spaces produce a rectangular or frankly convex appearance to the metacarpals, metatarsals and phalanges. Trabeculations of the medullary space give the bones a mosaic pattern *(Voskaridou et al., 2001).*

The skull shows marked widening of the diploic space and arrangement of the trabeculae in vertical rows giving "Hair-on-End" appearance.

Others are; failure of pneumatization of the maxillary sinuses and over growth of the maxilla. These changes lead to prominence of upper incisors and separation of the orbits, these are the classic thalassemic facies *(Chan et al.,2002).*

Other bony changes; include widening of the ribs with notching and development of masses of extramedullary haematopoietic tissue that may present as masses in the paravertebral region that may rarely lead to cord compression.

The vertebrae are square with course trabeculae. Compression fractures of the vertebrae may also occur *(Michelson et al., 1998).*

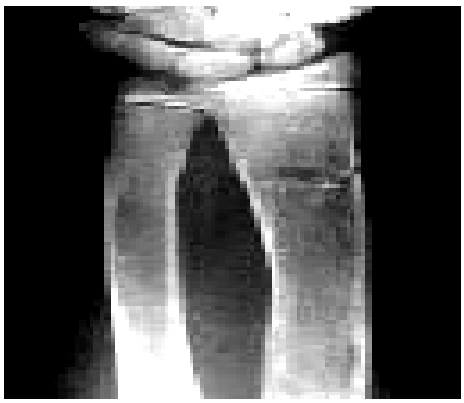


Fig.(5): Anteroposterior plain X ray of the forearm of a thalassemic patient showing fracture distal both bones forearm *(www.emedicine.com).*

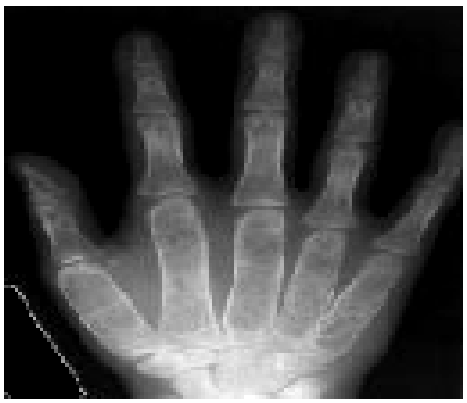


Fig (6): Anteroposteror plain X ray of the hand showing generalized loss of bone density *(www.emedicine.com).*

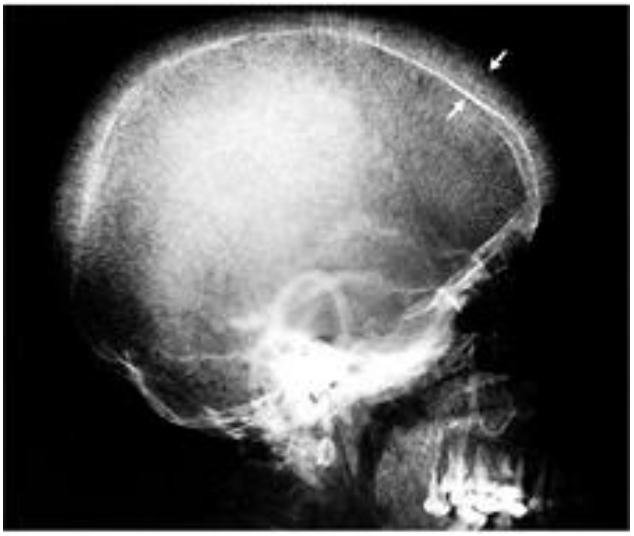


Fig (7): Plain X ray lateral view of the skull showing hair on end appearance *(www.emedicine.com).*

Fig. (8): Plain X ray anetroposterior view of lumbar vertebrae showing marked osteopenia *(www.emedicine.com).*

Screening for thalassemia

Because of the changing demography of disease in many countries the thalassemias will be a major health problem in the new millennium. As populations become richer, and standards of nutrition and public health improve, there is a fall in childhood mortality.

Hence, an increasing number of babies with genetic diseases such as thalassemia will survive the early months of life and present for treatment. It is essential, therefore, that some form of program for the population control of these diseases is initiated *(Shamshiraz et al., 2003)*.

If populations wish to offer marital choice, it is essential to develop premarital screening programs, which are best carried out on school children. However, it is vital to have a very well organized genetic counselling program in place and to provide both verbal advice and written information about the results of screening *(Weatherall, 1997)*.

The alternative approach is to screen every women of an appropriate racial background in early pregnancy, probably the most cost effective way of screening for thalassemia is through the red cell indices *(Leung et al., 2005)*

Red cell distribution width (RDW) which detects the heterogenecity of red cell size and anisocytosis in the blood smear are more sensitive indicators than mean corpuscular volume (MCV) to establish the possible origin of microcytic hypochromic anemia. Both should be used together in early diagnosis. The RDW is high in iron deficiency, but in most other conditions with microcytosis, RDW is normal *(Winichagoon et al., 2002)*.

Prenatal diagnosis:

Prenatal diagnosis is needed to prevent birth of thalassemic off spring to the couple at risk. Several techniques are available, the choice depending on the gestational age and the potential nature of the defect.

Initial attempts to identify foetuses at risk for thalassemia major depended on foetal blood sampling during the second trimester.

The application of recombinant DNA technology for carrier detection and prenatal diagnosis greatly enhanced its accuracy and availability *(Cao et al., 1998)*.

Fetal DNA is prepared from amniocytes obtained at 15 to 17 weeks of gestation or from chorionic villus sampling at 9 to 11 weeks. Fetal loss after the latter procedure (1 to 3) is similar to natural wastage for pregnancies of this duration. Fetal DNA may be amplified enzymatically by polymerase chain reaction (PCR), making it possible to provide specific diagnoses within 1 to 3 days *(Leung et al., 2005)*.

PCR also permits use of maternal blood as the source for fetal nucleated red cells if the genetic marker thought is present in the fetus but not in the mother. The technologic means selected for analysis of parental or fetal DNA is determined by the nature of the mutation thought.

The global development of prenatal screening programs in the early 1980s was monitored by the World Health Organization's International Registry for Prenatal Monitoring of Hereditary Anemias, providing a mechanism for the rapid dissemination of new knowledge *(Anderson et al., 2001)*.

These programs have had a major impact on the incidence of thalassemia major in parts of the world where its prevalence exceeded available resources. The combined efforts of screening couples at risk and prenatal diagnosis have reduced the birth rate of children with thalassemia major by 70 to 90% in Sardinia, Greece, Cyprus, and Ferrara *(Camaschella et al., 1990).*

Treatment of β thalassemia

The spectrum of the disease:

Since thalassemia is present in nearly all parts of the modern world, more interest has developed in the treatment of this group of disease. Therapeutic modalities for the supportive or curative treatment of thalassemia have been expanded, offered a wide variety of therapeutic options, some currently in use, others for future application.

Because of the very wide spectrum of disease severity and manifestations among patients with thalassemia intermedia as compared to thalassemia major, there is a significant amount of overlap in the use of the different types of therapy for these two types of patients.

The mainlines of treatment are still adequate transfusion, backed up by iron chelation therapy and the judicious use of splenectomy *(Deborash et al., 2000)*.

1. Transfusion therapy :

Patients who are able to maintain a hemoglobin concentration more than 7.5 gm/dL usually don't require chronic transfusion therapy.

Most patients with more severe grades of anemia require regular blood transfusion to facilitate growth and permit participation in normal activities. Regular transfusions should be started when the hemoglobin concentration falls below 7 gm/dL or when there is impaired growth *(Piomelli et al., 1995)*.

Before transfusion we should determine the blood group of the patient completely to identify minor red cell

antigens, pretransfusion laboratory tests including a complete blood cell count, differential cross match and red cell antibody screen.

Height and weight are recorded at least every 3 months. Liver functions tests (ALT, AST and bilirubin) are evaluated every three months and serum ferritin is evaluated every 3-6 moths *(Nathan et al., 1998)*.

Maximum effectiveness of Transfusional therapy depends on the availability of safe blood.

Choice of the Scheme for Blood transfusion in thalassemia major:

❖ intermediate Schemes:

Mean Hb 9-10 gm/dL are acceptable in terms of daily living.

❖ Hypertransfusion Schemes:

Mean Hb 10 gm/dL or greater, improve the quality of life without accelerating the lethal complications of iron overload, also suppress erythroid activity and prevent the unlimited bone marrow expansion that underlies the skeletal pathology of thalassemia major.

Additional advantages of a regular transfusion program include prevention or delay in the development of congestive splenomegaly, fewer severe infectious illness *(Cazzola et al., 1997)*.

❖ Supertransfusion Program

Maintenance of mean hemoglobin levels at 11 to 12 gm/dL. Hemoglobin value is never allowed to drop below 12 gm/dL and is raised regularly to 14 gm/dL by transfusion every 2-3 weeks. Super-transfusion permits an

excellent quality of life and suppression of the bone marrow thereby shrinking the bone marrow mass and reducing the blood volume by approximately 20%. Reduction of the blood volume, in turn, permits the maintenance of a higher hemoglobin concentration without an increase in the transfusion requirement within 1-4 months of raising the minimum hemoglobin value to 12 gm/dL. The transfusion requirement returns to that amount necessary to maintain a minimum level of 9 gm/dL *(Rund et al., 2000).*

Complications of Transfusion Therapy:

a. The primary long term complication of blood transfusion is iron loading and resulting parenchymal organ toxicity *(Nathan et al., 1998).*

b. Febrile reactions to leukocyte antigenic determinants and allergic reactions to plasma components are commonly encountered in chronically transfused patients. Washing of red cells in saline or the use of microaggregate filtration to remove leukocytes can be beneficial *(Nathan et al., 1998).*

c. The transmission of viral infections by transfusion is a serious problem in chronically transfused patients. These viral infections include: hepatitis B, hepatitis C and HIV. The most important consideration regarding this problem is the use of blood products screened for the presence of potential infectious agents *(Nathan et al., 1998).*

2. <u>Chelation therapy :</u>

Most patients with thalassemia major die from complications of iron overload. At a total body iron burden of 40 gm, organ function begins to fail, and at 60 gm or

more, intractable cardiac failure has its onset *(Jensen et al.,1997).*

Types of chelation:

a. Defroxam (parental chelation)

The most effective iron chelating agent widely available is defroxamine, a siderophore produced by streptomyces pilosus.

It is a complex hydroxylamine with a remarkable affinity for iron. Desferrioxamine enters cells, chelates iron, and appears in serum and bile as the iron chelate produce feroxamine *(Hoffbrand et al., 1998).*

The optimal age for starting this program has not been established. Some reports describe success in children as young as 2-4 years, but there may be an adverse effect on growth. Many centers wait until the patients is 5-6 years old, when significant iron excretion can be accomplished and patient cooperation is better *(Williams, 2001).*

It is recommended that desferrioxamine be started after the first 10 to 20 transfusions or when the serum ferritin reaches 1000 μg/ml. In general, these criteria are reached at about 3 years of age.

When given before 3 years of age, it is given at a reduced dose (20 to 30 mg/kg/day) to prevent the drug's adverse effect on linear growth. After 3 years of age, the dose of desferrioxamine is about 40 to 50 mg/kg/day. Dose of desferrioxamine in excess of 50 to 60 mg/kg/day are associated with visual and auditory neurotoxicity *(Styles et al., 1996).*

The patients are advised to use the drug at least 5 to 6 days per week; this promotes urinary excretion of 15-60 mg of iron per day *(Olivieri el al., 1997)*.

The requisite amount of drug is given most conveniently with a small portable infusion pump that permits delivery of microliter quantities of the drug subcutaneously from a standard syringe through a butterfly needle placed by the patient in the anterior abdominal wall.

The total daily dose is infused over an 8 to 12 hour period at night, allowing freedom from the device during daylight hours *(Chan et al., 2001)*.

Study done by Hagogi et al. (2001) concluded IV administration of high dose (DFO) over 48 h/w using portable pump, implanted chamber, improve compliance in two thalassemic adult patient with dose 198 mg/k/d, 170 mg/kg/d respectively with significant decrease in iron overload serum ferritin from 2967 to 457 µg/L and 6476 to 1951 µg/L respectively.

It is now clear that DFO can be toxic when given in excess dose. It can have neurological side effects, affecting sensorineural function (visual, hearing), other side effects are seen in skeletal system as decrease growth velocity. So close monitoring is instituted and becomes routine in each individual patient *(Olivieri et al., 1997)*.

b. Oral chelators :

i) Salicyl hydroxamic acid "SHAM" is a compound composed of salisylate moiety and hydroxamic acid moiety, the antibacterial activity of the hydroxamic acid is due to its interaction with bacterial deoxyribonucleic acid. *Khalifa et al. (1994)* found that

increasing dose of SHAM to 40 mg/kg/day has led to a significant increase in the urinary iron excretion, but is still lower than that excreted by the same dose of subcutaneous desferrioxamine.

A combined therapy composed of subcutaneous desferrioxamine in a dose of 40 mg/kg/day and oral SHAM in a dose of 40 mg/kg/day markedly increases the urinary iron excretion *(Raiola et al., 2003)*.

ii) Deferiprone:

An orally active iron chelator. The agent most extensively assessed is 1, 2, dimethyl-3-hydroxypyridin-4- one (deferiprone LI). Deferiprone has high affinity for iron and interacts with almost all the iron pools at the molecular, cellular, tissue and organ levels. 75 mg of deferiprone, per kg body weight induces urinary iron excretion approximately equivalent to that achieved with 30-40 mg of desferrioxamine per kg *(Maggio et al., 2002)*.

All the adverse effects of deferiprone arc considered reversible, controllable and manageable. These include agranulocytosis, neutropenia, musculoskeletal and joint pains. Discontinuation of the drug is recommended for patients developing agranulocytosis *(Kontoghiorghes et al., 2003)*.

iii) Combination:

For the purpose of iron trapping, it is possible that a combination of different types of chelators, such as L1 plus desferrioxamine, may chelate iron more successfully that a single drug. Deferiprone was administered orally three times daily, in combination with 8 h of nightly subcutaneous desferrioxamine. A 24-129% increase in iron excretion using the combination was found, compared to desferrioxamine alone *(Hoffbrand et al., 1998)*.

iv) Drugs:

One of the newer drugs is HBED (N,N'-bis 2-hydroxybenzyl ethylenediamine-N,N'-diacetic acid), a polyanionic amine. This drug was initially reported as effective in oral form, though later reports were less encouraging. Recently, a report has appeared suggesting that the drug has therapeutic potentials. HBED given either subcutaneous bolus or 20 mm IV infusion. By both routes was twice as efficient as DFO in producing iron excretion, but SC administration more efficient. No systemic toxicity was found but local irritation was found at some sc injection sites. With decrease dose no local irritation was found. In addition HBED can act both as an H-donating antioxidant and as effective chelator lacking pro-oxidant capacity *(Samuni et al., 2001)*.

3. Induction of Fetal haemoglobin:

The rational for administration of various drugs to augment the production of fetal hemoglobin is based on the observation that in patients with hereditary persistence of fetal hemoglobin, the α/non-α chain synthesis ratio is balanced, resulting in longer red blood cell survival *(Olivieri, 1998)*.

Hydroxy Urea:

The first studies, were disappointing, later, individual case reports showed marked improvement in hematological parameter in TI. This seemed mainly to result from an increase in HbA, rather than HbF. In summary, it is clear that rare patients with thalassemia intermedia or even more rarely, with thalassemia major can respond dramatically to HU with a decrease in transfusion requirement *(De Paula et al., 2003)*.

However the potential usefulness of HU for the majority of transfusion dependent thalassemia major patients is not clear at present, in contrast to its proven value in ameliorating sickle cell disease *(Alebouyeh et al., 2004)*.

Erythropoietin:

The administration of large dose of erythropoietin has been shown to augment HbF production. This prompted clinical trials using recombinant human erythropoietin in thalassemia. However, it was found that, using large doses of erythropoietin (500-950 IU/k, three times a week), the level of total HbF was significantly raised in some patients. Studies suggested that splenectomized patients respond better *(Rund et al., 2000)*.

4. Splenectomy:

Progressive splenomegaly shortens red cell survival, increases the transfusion requirement and accelerates iron loading. Splenectomy should reduce red cell requirements by 30% in a patient whose transfusion index (calculated by addition of the total of packed cells administered over 1 year, divided by mid year weight in kg, exceed 240 ml/kg/year) *(Martin e al., 2001)*.

Splenectomy should usually be delayed until the age of 5 or 6 years. At least 2-3 weeks prior to Splenectomy polyvalent anti-pneumococcal, anti-meningococcal, and anti-hemophilus influenzae type B vaccines should be administered (*Atkinson et al., 1996)*. Oral penicillin therapy, used as prophylaxis against post Splenectomy infection is

now generally given to splenectomized patients with thalassemia *(Olivieri et al., 1999)*.

Study by *Sarkar et al. (2001)* concluded Splenectomy with slice grafting of the spleen, noticed good immunity and good fate of graft.

5. Bone marrow Transplantation:

Conventional Allogeneic BMT:

The decision to perform allogeneic bone marrow transplantation is generally considered appropriate only for those patients who have a fully HLA-matched donor (at most, 30-40% of all patients) *(Rund et al., 2000).*

Outcomes after transplantation are greatly influenced by the presence of hepatomegaly, portal fibrosis and ineffective chelating therapy before transplantation. Children without any of these risk factors have rates of survival and disease free survival exceeding 90% three years after transplantation (those identified as class 1).

By contrast, in those with all three risk factors, (class 3 patients) the rates are approximately 60%. In patients with either hepatomegaly or portal fibrosis (class 2), the event free survival rate is approximately 80% *(Olivieri et al., I999)*.

Umbilical Cord Blood Stem Cell Transplantation:

Stem cell transplantation is currently the only curative therapy. Bone marrow transplantation offers a high probability of cure when performed in young children. The alternative use of stem cell from cord blood makes possible earlier transplant with better chance of cure, although the engraftment is slower compared to bone marrow transplantation *(Issaragrisil, 2002).*

Intrauterine Bone Marrow Transplantation:

A small number of centers have begun to perform intrauterine bone marrow transplantation, with either fetal liver or bone marrow derived stem cells as the source of hematopoietic stem cells.

At present, sustained, successful intrauterine transplantations have been reportedly performed only for congenital immunodeficiency syndromes, such as bare lymphocyte syndrome. Such procedures have not yet been performed successfully for thalassemia *(Hayward et al., 1998)*.

6. Gene Manipulation and Gene Replacement:

The interaction between β-thalassemia and genetic syndromes that increase γ-globin synthesis has illustrated that even small increases in γ-globin production lead to a significant improvement in the effectiveness of red cell production in patients with β-thalassemia *(Rund et al*., 2000).

Three general strategies have been considered as methodologies to perform genetic therapy for β-thalassemia:

- The first is gene transfer, the addition of an exogenous gene to human hematopoietic cells. By far the most common method used towards this goal has been viral mediated gene transfer. A number of vector types have been used retroviruses and adeno-associated viruses are the most common ones.

- The second variation in the strategies of genetic therapy of thalassemia is the use of various molecular biological tricks to either correct the DNA, thereby correcting the mutation, or by correcting the mutant RNA transcript. One

such novel strategy exploits the cell's own repair mechanisms, by introduction of oligonucleotides targeted to specific regions in the DNA double helix which contain mutations.

- A final strategy of the genetic therapy of thalassemia involves the use of methods to down regulate the output of the α-globin gene, reducing chain imbalance. This method can be most useful for the treatment of thalassemia intermedia in which there is sufficient β-globin gene output as a baseline *(Deborash et al., 2000)*.

Neurological complications of hemolytic anemias

Over the years, several reports have demonstrated involvement of the nervous system in β-thalassemia patients. Neurological complications have been attributed to various factors such as chronic hypoxia, bone marrow expansion, iron overload, and desferrioxamine neurotoxicity.

In most cases, neurological involvement does not initially present with relevant signs or symptoms (i.e., is subclinical) and can only be detected during neurophysiological or neuroimaging evaluation *(Ameri et al., 2003)*.

Central nervous system complications like convulsions, transient ischemic cerebral attacks, headaches, deafness, paresthesias, hyporeflexia, hemiplegia, and hemiparesia have been reported rarely in thalassemia major.

These findings have been attributed to the release of vasopressins after multiple transfusions, leading to hypertension, encephalopathy and hemorrhage or to chronic anemia-hypoxia *(Pignatti et al., 1998)*.

With a better knowledge of natural inhibitors of coagulation, it is now known that there is an increased tendency to thrombosis in hemolytic anemias, especially in thalassemia major and sickle cell anemia. It has been reported by various investigators that deficiencies of protein C (PC), protein S (PS) and antithrombin III (AT III) have some role in this prothrombotic tendency.

This deficiency may be manifested by stroke, convulsions and thromboembolic episodes *(Akar et al., 2000)*.

Abnormal findings in the visual, auditory, and somatosensory evoked potential recordings are mainly attributed to DFO neurotoxicity. On the other hand, nerve conduction velocity abnormalities are associated either to chronic hypoxia and older age or to hemosiderosis, whether by means of pancreas involvement or not *(Zafeiriou et al., 2006)*.

Neuromuscular complications of thalassemia are not common. One third of patients on moderate transfusion regimen were noticed to have delayed walking beyond 18 months.

Some patients developed a curious myopathic syndrome with proximal weakens mostly in the lower extremities, and a myopathic electromyographic pattern. This complication was associated with severe skeletal stigmata, suggesting that it occurred in inadequately transfused patients *(Swenson, 1999)*.

Spinal cord compression due to extramedullary hematopoiesis is one of the rare but important complications of thalassemia *(Cianciulli et al.,2000)*.

Spinal cord compression due to extramedullary hematopoiesis :

Hint on the anatomy of the spinal cord :

The spinal cord is a long, cylindrical structure located in the vertebral column that extends from the foramen magnum at the base of the skull to the level of the first lumbar vertebrae. It is part of the central nervous system and is approximately 1cm in diameter, 42-45cm long and weighs around 30 grams. The spinal cord provides a two way conduction pathway, conducting sensory and motor impulses to and from the brain and controlling many reflexes.

There are 31 pairs of spinal nerves that leave the spinal cord at regular intervals: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal *(Harkess, 2003)*.

The spinal cord is protected by bone, cerebrospinal fluid and the meninges. The vertebrae (7 cervical, 12 thoracic, 5 lumbar, 1 sacral and 1 coccyx) support the body, the vertebral column surrounds and protects the spinal cord. The meninges are membranes that cover the brain and the spinal cord, there are three: the dura mater (outer), arachnoid (middle) and pia mater (inner) *(Daisy et al.,2001)*.

The space between the vertebral column and the outer surface of the dura mater is called the epidural space. The subdural space is next between the inner surface of the dura mater and the arachnoid membrane. Below this is the subarachnoid space, this lies between the arachnoid membrane and the pia mater and is attached to the spinal cord. The cerebrospinal fluid is located in the subarchnoid space which begins in the brain and continues down the spinal cord *(Wagner, 1997)*.

Extramedullary hematopoiesis is a common manifestation in a variety of hematological disorders such as severe anemia, leukemia, hereditary haemoglobinopathies, osteosclerosis, carcinomatosis, Hodgkin's disease, conditions following hemorrhage, hereditary spherocytosis, erythroblastosis foetalis and myelofibrosis *(Chute et al., 2004)*.

In the above conditions production of blood elements by bone marrow is insufficient for the demands of the circulation. Because of this organs such as liver, spleen and lymph nodes and rarely other tissues such as thymus, adrenal cortex, lungs and pleura, appendix, dura mater, breast, sciatic nerve, retroperitoneum and paravertebral area of the thorax became sites of extramedullary hematopoiesis *(Aliberti et al., 2001)*.

In thalassemic patients extramedullary hematopoiesis is a relatively common finding with or without symptoms depending on its site. Intrathoracic extramedullary hematopoiesis in these patients is found in a small percentage of 11-15% of patients. In an even smaller percentage intrathoracic masses can compress the spinal cord and cause neurological symptoms *(Forget, 2000)*.

The thoracic region and, to a lesser degree, the lumbar level are the preferred sites for the extramedullary masses. The reason for this predilection is uncertain. As the subarachnoid space of the spinal canal is narrower in the thoracic region, even a relatively small mass in this region could cause cord compression. Nevertheless, the majority of patients with intrathoracic extramedullary hematopoiesis remain asymptomatic *(Tze et al., 2002)*.

A number of mechanisms have been postulated to account for the predilection for involvement of the thoracic region in spinal EMH. These include extension of EMH tissue through

the thinned trabeculae at the proximal rib ends, direct expansion from adjacent vertebral bone marrow, and development of EMH tissue from branches of the intercostal veins, the narrow central canal and limited mobility of the thoracic spine predisposes itself lo spinal cord compression *(Tze et al., 2002)*.

Intrathoracic extramedullary hematopoiesis is generally localised at the posterior mediastinum, and the middle and lower paravertebral *(Sule et al., 2003)*.

Spinal cord compression due to extramedullary hematopoiesis mostly occurred in thalassemia intermedia, despite chronic anaemia there is no need for repeated blood transfusions. Haemoglobin concentrations are between 6-9 gm/dl. At adult age pathological fractures and thoracic mass lesions consisting of hematopoietic tissue can be seen. Spinal cord compression due to intrathoracic EMH is extremely rare *(Sule et al., 2003)*.

Signs and Symptoms of spinal cord compression:

Clinical features of spinal cord compression depend on extent and rate of development of cord compression.

- ❖ Pain: Back pain is usually the first symptom of SCC, it is often constant, dull, aching and sometimes radiating. The pain may increase or progress slowly, it is often referred to as crescendo pain (pain that waxes and wanes). It is exacerbated by movement, especially when flexing the neck or raising the legs, coughing, sneezing, or straining. It is not relieved by lying down although it can be sometimes relieved by sitting the patient upright. Leg pain may occur and be unilateral or bilateral in nature that radiates from the back *(Salehi et al., 2004)*.

- ❖ Motor Weakness: This usually follows pain, the time frame for this sign is often variable, from hours to days, weeks or months. Patients may experience stiffness and heaviness of the affected extremity, they may present with an unsteady gait or ataxia (failure of muscle co-ordination) and foot drop.
  - Cervical spine disease produces quadriplegia.
  - Thoracic spine disease produces paraplegia.
  - Lumbar spine disease affects L4-L5 and sacral nerve roots *(Markman, 1999)*.

- ❖ Sensory Impairment: This usually follows motor weakness; symptoms include loss of sensation, numbness, tingling and coldness in the affected area.

- ❖ Autonomic dysfunction: This will occur if the SCC progresses. Loss of bladder control results in urinary retention, frequent small voids, overflow or incontinence. Loss of bowel control such as the urge

to defecate, may lead to constipation or incontinence. Loss of sphincter control is often a later sign that is associated with a poor prognosis.

Sexual impotence may also manifest. Without identification of the above signs and symptoms and a delay in the appropriate treatment, complete and irreversible paraplegia may develop within hours to days *(Harkess, 2003)*.

❖ Tendon reflexes are often :

- Increased below level of compression.
- Absent at level of compression.
- Normal above level of compression *(Abraham, 1999)*.

❖ Cauda equina compression due to central disc prolapse below the level of L2. The bundle of nerves extending from the bottom of the spinal cord is called the equina because it resembles a horse's tail. The symptoms that result are called the cauda equina syndrome *(Gleave et al.,2002)*.

Pain is felt in the lower back, but sensation is reduced in the area of the body that would come in contact with a saddle (a condition called saddle anesthesia), including the buttocks, thighs, bladder, and rectum. Other symptoms include erectile dysfunction (impotence), urinary incontinence at night, loss of reflexes in the ankle, if compression is great enough, bladder and bowel function may be lost. People who have this syndrome require immediate medical attention. The disorder causing the compression is called cauda equina syndrome *(Gleave et al.,2002)*.

Differential diagnosis of spinal cord compression:

- Tumors (primary and secondary).
- Degenerative disease (i.e. disc prolapse and osteoporosis).
- Autoimmune disease (i.e. transverse myelitis and Guillan Barre).
- Infection (i.e. discitis and Pott's disease of the spine).
- Traumatic *(Daisy et al. , 2001).*

Diagnosis:

History: The history is the key to the evaluation of spinal lesions. If pain is the presenting symptom, the physician must ask about the location, radiation and duration of the pain. The physician should also ask about the specific characteristics and severity of pain and whether the pain is present at night.

It is also important to inquire about factors that exacerbate or relieve pain and other symptoms. Radicular pain may direct the evaluation to a specific nerve root level. The patient should be asked about paresthesias, numbness or weakness. Muscle weakness if progressive, must be evaluated urgently. Bowel and bladder symptoms with perianal numbness may be indicative of cauda equina syndrome, a true emergency that requires urgent decompression (*Ratliff et al., 2001)*.

Clinical suspicious may be raised by a history of thalassemia and auxiliary evidence of extramedullary hematopoiesis *(Bueff et al., 1996)*.

Physical examination:

The physician should examine the entire spine for areas of redness, scars, blisters, lipomata, hairy patches, birthmarks and cafe-au-lait spots. The spine should also be palpated for bony abnormalities, deviation from the midline and tenderness *(Daisy et al., 2001)*.

Range of motion, including flexion, extension, lateral rotation and lateral bending, should be assessed. In general, patients with disc disorders have pain with forward flexion, whereas patients with spinal stenosis have pain with extension of the lumbar spine. Gait should also be assessed.

The patient should be asked to toe walk and heel walk as part of the evaluation of motor strength.

An important aspect of the physical examination is a rectal examination to assess sphincter tone, especially if the patient mentions bowel or bladder dysfunction. The physician should perform a systematic, thorough motor and sensory examination of the patient's extremities *(Daisy et al., 2001)*.

Chronic mild neurological deficits involving a single nerve root may not necessarily be considered a red flag because these deficits are common in patients with degenerative pathologies such as disc herniation and lateral stenosis (*Ratliff et al., 2001)*.

However, a more aggressive approach is required when a patient has progressive neurological deficits. Babinski's sign and hyperreflexia are widely understood to be cardinal signs of the upper motor neuron syndrome that typically occurs in spinal cord compression. The physician should be aware that, if present, a positive (abnormal) Babinski's sign is helpful, but a negative or absent sign does not exclude severe disease *(Swensen, 1999)*.

Investigations:

A. Laboratory Tests:

The laboratory evaluation includes a complete blood cell count with differential, an erythrocyte sedimentation rate and a urine analysis. The findings of the clinical evaluation may indicate the need for other specific tests *(Daisy et al., 2001)*.

B. Imaging studies:

Imaging studies are extremely important in the evaluation of spinal cord compression. Computed tomographic (CT) scanning, magnetic resonance imaging (MRI), myelography and combined CT and myelography can clearly define anatomy. However, these studies are costly *(Habibzadeh et al., 2005)*.

1) Plain X-ray:

In spinal cord compression due to extramedullary hematopoiesis plain radiographs often reveal well demarcated paraspinal masses and bony changes associated with chronic anemia such as trabeculations, widened ribs or thickened clavicle *(Tunaci, et al., 1999)*.

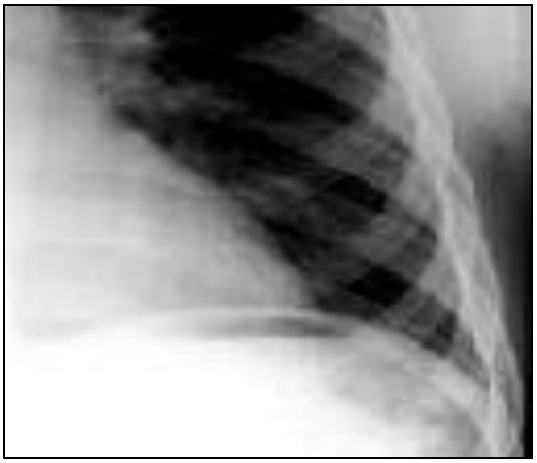
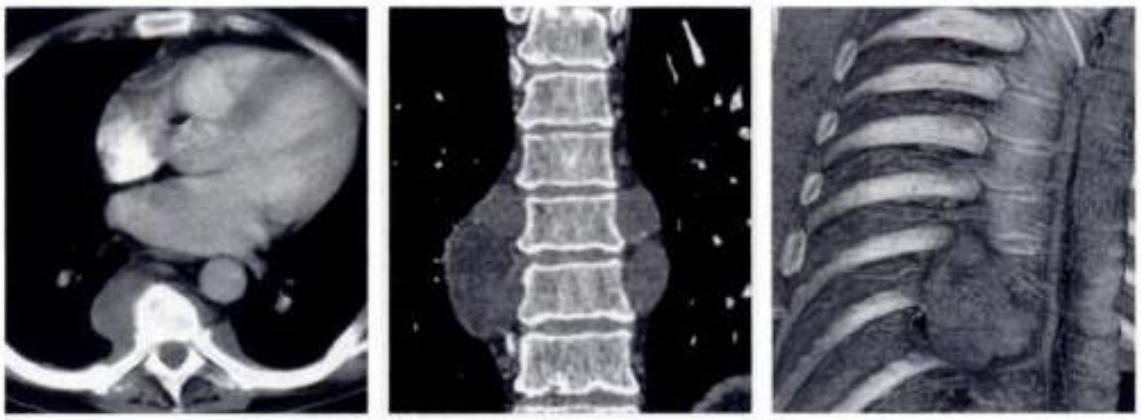


Fig. (9): Plain X ray chest showing long linear density within the medulla of the ribs.

2) CT scan:

CT is a valuable investigation for patients in whom MRI is contraindicated or unavailable. CT scanning is less expensive than MRI. CT scans provide better imaging of bony structures. Hence, CT scanning is considered the imaging modality of choice to evaluate patients for spinal trauma and vertebral fractures. CT scanning is less sensitive to patient movement than MRI, and it can be used in patients with pacemakers, ferromagnetic vascular clips and other implanted devices *(El Bahri et al., 2003)*.

By CT foci of extramedullary hematopoiesis appear as convex paravertebral masses of soft tissue density the masses usually extend downward for several vertebral segments below T7 and may have a subpleural component. Unlike neurogenic tumors hematopoietic masses do not cause pressure erosion to bone *(Tsitsopoulos et al.,2007)*.



A B C

Fig.(10) : (A)CT thoracic spine show extramedullary hematopoiesis manifested by paravertebral masses of soft tissue density at the level of lower thoracic spine. (B) cronal reformation. (C) paraspinal masses in another patient.

On CT active lesions show high density and are enhanced with a contrast injection. Non active lesions are hypodense as they contain fatty substances and do not show contrast enhancement *(Chute et al., 2004)*.

In high risk patients with severe impairment of the skeleton, splenectomy, more severe anemia or in the presence of suggestive modifications of peripheral blood, as the progressive increase of the erythroblasts, reticulocytes and indirect bilirubin, but with a not suitable decrease of the Hb level, CT screening should be considered *(Radu et al., 2005)*.

3) MRI:

Although of its relative high cost, MRI is currently the gold standard for demonstrating spinal EMH. The advantages of MRI are several:

1. Non invasive and doesn’t involve radiation.

2. It allows multiplanar imaging.
3. Produces superior soft tissue delineation with high sensitivity.
4. It covers a large area of the spine and can show changes within the disc and vertebral body.
5. It allows evaluation with high accuracy and shows the possible extension of the disease into the intra spinal space *(Tze et al., 2002)*.

On MRI, EMH tissue possesses signal intensity similar to that of the adjacent red marrow in the vertebral bodies. Gadolinium enhancement is minimal or absent, differentiating it from other epidural lesions such as abscesses or metastases *(Tsitouridis et al., 1999)*.

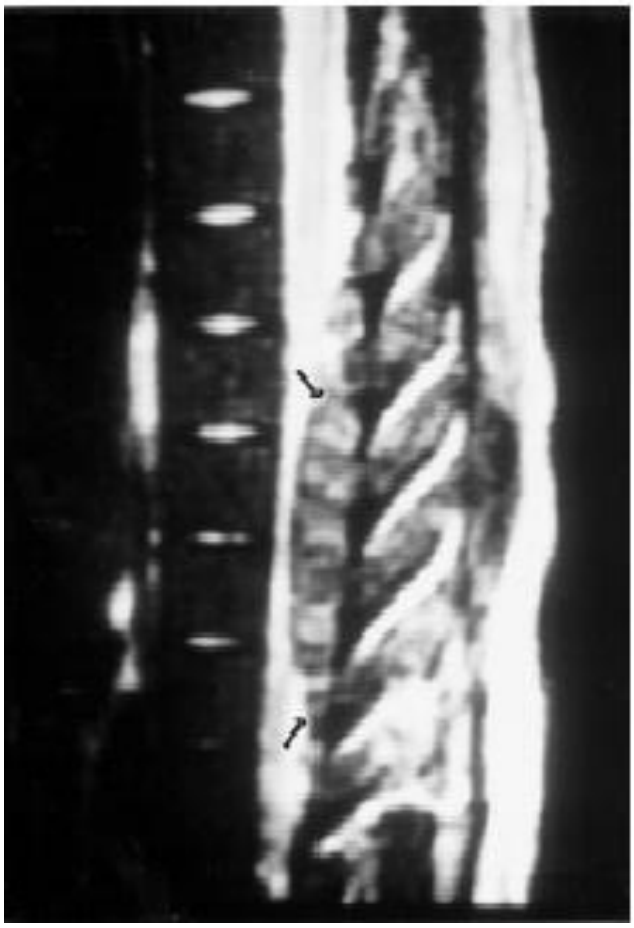


Fig. (11): Sagittal magnetic resonance imaging, at diagnosis, demonstrating posterior epidural mass with compression of the spinal cord from T4 through T8 (arrows) *(Silvana et al., 1998)*.

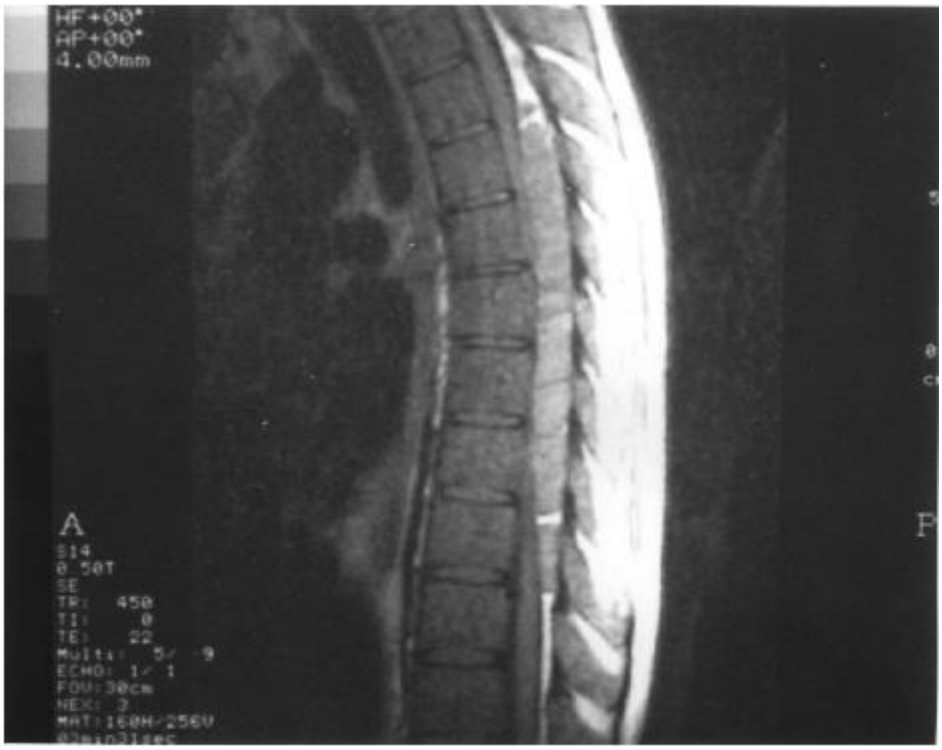


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Fig. (12): MRI of the thoracic spine of a patient with thalassemia intermedia shows multiple, lobulated mass lesions not showing any calcification and without any bone destruction were present at the third and seventh thoracic levels on the posterior side *(Sule, 2002)*.

On MRI, active lesions show hypointense signals both onT1 and T2 weighted images, but during the remission phase they show hyperintense signal. A peripheral ring having hyperintense signals is a pathognomonic finding *(Tsitsopoulos et al.,2007)*.

Using the magnetic resonance images in the fast sequence results in a myelography-like appearance that allows rapid screening of the spinal canal with high sensitivity for epidural masses *(Tung et al., 1999)*.

4) Myelography:

Myelography is declining in popularity due to its invasiveness, the need for cisternal puncture in cases of complete block preventing passage of radiographic contrast, and reports of neurological deterioration following the procedure *(Para et al., 1995)*.

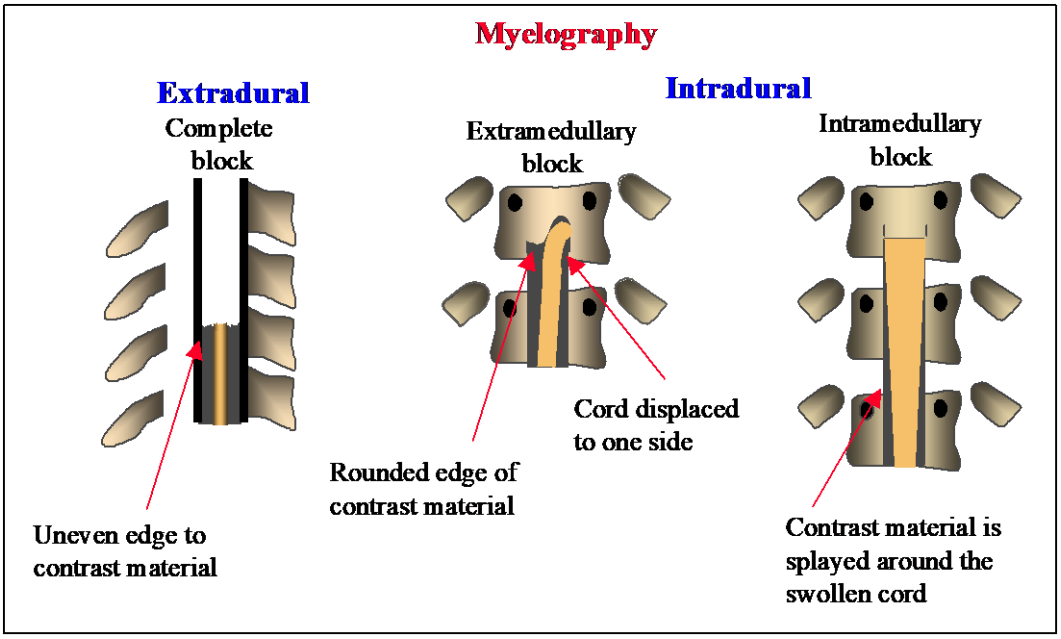


Fig.(13) : Illustration of different causes of SCC in myelography.

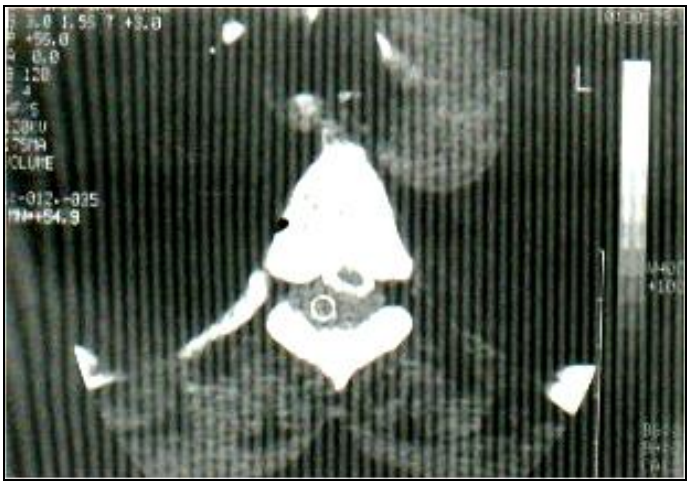


Fig. (14): CT myelogram in axial view, at the T6 level shows a large posterior extradural tissue mass, producing compression and anterior displacement of the spinal cord *(Ben Rejab et al., 1999)*.

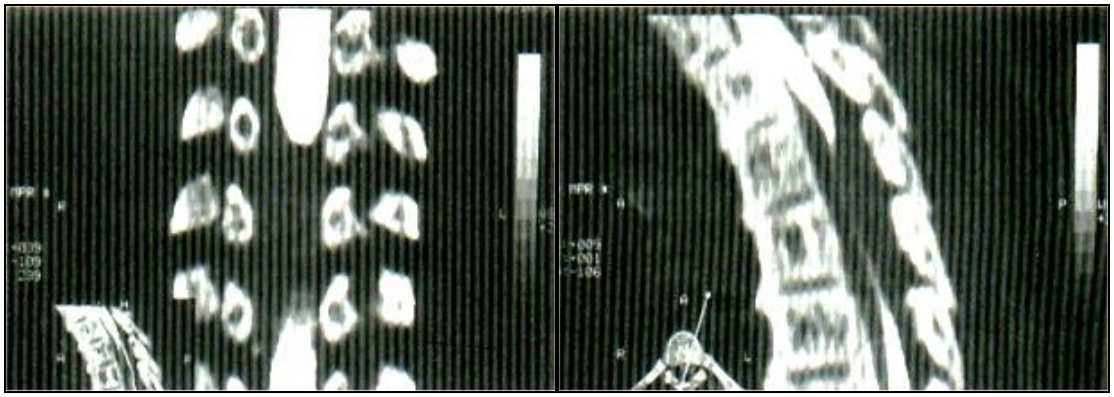


Fig. (15): Frontal and sagittal reconstruction of CT myelography show the level of the compression and the extension of the lesion *(Ben Rejab et al., 1999)*.

CT guided needle biopsy of paraspinal masses is possible for tissue diagnosis, but the procedure carries the risk of catastrophic hemorrhage and is therefore not usually advocated.

5) Bone scanning

Bone scanning can be useful when plain-film radiographs of the spine are normal but the clinical findings are suspicious for osteomyelitis, bony neoplasm or occult fracture.

Although bone scanning is a sensitive screening tool for bony tumors and infections, results are false-positive in one third of older patients who are at highest risk for these conditions and have a high incidence of osteoarthritis *(Moellers et al., 2002)*.

Tc99 bone scan has been used to diagnose paraspinal EMH but the diagnosis within the epidural space may be difficult due to the proximity to bone marrow*(Haldeman, 1996)*.

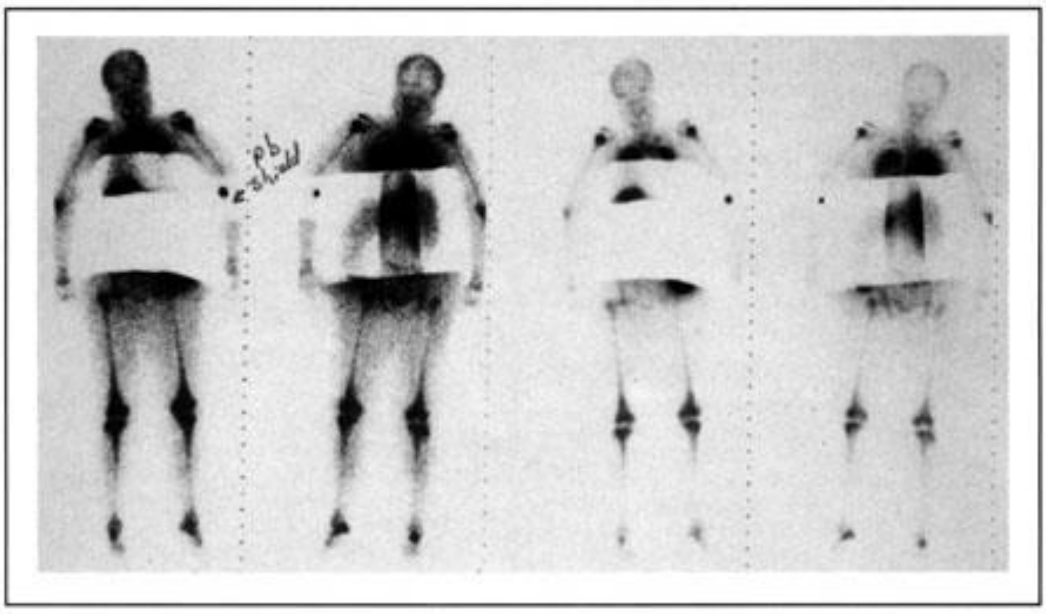


Fig. (16): Tc99 scan, demonstrating increased uptake throughout thoracic cavity.

Treatment of spinal cord compression due to extramedullary hematopoiesis:

Considerable controversy exists regarding the ideal treatment of SCC due to EMH. Management options include surgery, transfusional therapy, radiotherapy or any combination of these modalities. More recently the use of drugs such as hydroxyurea which act by enhancing hemoglobin levels has been reported *(Cianciulli et al., 2000)*.

Blood transfusions relieve chronic anemia and suppress extramedullary haemopoiesis. It has been used as the principal treatment modality in cases of spinal EMH where surgical decompression or radiotherapy were contraindicated e.g. pregnancy or severe anaemia. While blood transfusion may prevent further progression of EMH, it is unable to reverse preexisting cord compression. Its role in the management of patients with symptoms of acute onset is therefore limited. However it is a useful adjuvant treatment after surgical decompression *(Phupong et al., 2000)*.

Radiation therapy (RT) alone has been reported to yield excellent results with neurological improvement observed as soon as 3-7 days after initiation of treatment. Haemopoietic tissue is extremely radiosensitive and undergoes shrinkage after RT, with a decrease in volume by as much as 16.4%. Dosages reported in the literature range from 900-3500 rads *(Jackson et al., 1998)*.

However, some concerns about the use of radiotherapy have to be considered:

1) A risk of late side effects after irradiation of spinal cord and mediastinal organs cannot be excluded.

2) A relapse of the ectopic haematopoiesis after radiotherapy was reported in a substantial number of patients, especially if the underlying conditions did not change.

3) Other clinical symptoms such as weakness, fatigue and bone pains are not relieved by radiotherapy alone *(Radu et al., 2005)*.

Therefore, it is suggested that the treatment of EMH should begin with radiotherapy, which is necessary for a rapid decrease of the pseudotumours for preventing the risk of the compressive sequellae.

The combination of blood transfusion and radiotherapy is another therapeutic option. This has been recommended in cases in which there is recurrence after a single treatment (blood transfusion or radiotherapy), or for better results from the very beginning *(Aliberti et al., 2001)*.

Laminectomy is indicated in cases of acute presentation which do not respond to adequate transfusion or radiotherapy. Surgery confers the benefits of immediate relief of cord compression and histological diagnosis. Disadvantages include the risks of operating on anemic individuals who are predisposed to shock, incomplete excision in cases of diffuse involvement, instability and kyphosis associated with multilevel laminectomy *(Tze et al., 2002)*.

New advances in the treatment of thalassemia include the use of drugs such as hydroxyurea, sodium butyrate and erythropoietin which boost hemoglobin levels. Patients with spinal EMH have been successfully treated with hydroxyurea alone or in conjunction with transfusion therapy *(Alebouyeh et al., 2004)*.

Hyroxy urea (HU), a potent ribonucleotide reductase inhibitor and a cell cycle-specific agent that blocks DNA

synthesis, is a well known chemotherapeutic agent which has been used largely for the treatment of various myeloproliferative conditions over the past 20 years.

HU is easy to use because its main toxicity, i.e., leukopenia and thrombocytopenia, is usually fully reversible a few days after its discontinuation. *(Bradai et al.,2003)*.

The mechanism of action of HU in these cases is not completely understood but it is proved that it increases the efficacy of erythropoiesis by induction of HbF synthesis via a reactivation of γ-genes as a result of increased transcription and more efficient processing of the respective gamma-mRNA57*(De Paula et al., 2003)*.

Consecutively, a reduction of the α-globin chain excess results, leading to an elevated total Hb concentration without expansion of the erythroid marrow.

The successful treatment with HU in thalassemic patients with EMH may lead to the disappearance of the ectopic masses and to independence from regular transfusion therapy, without further extraosseous expansion of the haematopoietic tissue *(Wang et al., 2002)*.

However, in accordance with the opinion of *Cario et al. (2002)* that due to the potentially associated risks and the limited experience with this drug in thalasemic patients, the use of HU should be restricted to patients with severe clinical problems such as extended and symptomatic EMH, severe osteoporosis or transfusion-requiring therapy complicated by alloimmunization.

Patients and methods

Study population:

Our study included 60 patients with chronic hemolytic anemia (β thalassemia) recruited from the regular attendee of the Hematology Clinic Pediatric Hospital, Ain Shams University.

The study was conducted during the period of March 2006 to December 2006.

All patients were divided into 4 groups:

- Group A :

  17 Patients with Beta thalassemia major aged less than 15 years, they were 12 males and 5 females, their ages ranged from 7 – 15 years old with a mean of 10 ± 2.5 years old.

- Group B :

  23 Patients with Beta thalassemia major aged more than 15 years, they were 12 males and 11 females, their ages ranged from 15 – 30 years old with a mean of 20 ± 2.8 years old.

- Group C :

  10 Patients with Beta thalassemia intermedia aged less than 15 years, they were 5 males and 5 females, their ages ranged from 6 – 15 years old with a mean of 9 ± 2.6 years old.

- Group D :

  10 Patients with Beta thalassemia intermedia aged more than 15 years, they were 3 males and 7 females their age ranged from 15 – 20 years old with a mean of 17 ± 2 years old.

All patients were attending the haematology clinic for regular blood transfusion and follow up. Our patients were on transfusion therapy with packed RBCs except for 8 patients of group C without blood transfusion.

Most of our patients were on chelation therapy with Desferral, except for 8 patients who were switched on oral chelators and 6 patients with thalassemia intermedia without chelation therapy.

Methods:

All patients were subjected to the following:

A. A structured questionnaire was planed to fulfil the following data:

a. Demographic data :

   Name, age, sex, address, consanguinity, socioeconomic class.

b. Transfusional history:

   - ❖ age of first transfusion,
   - ❖ amount of blood in every transfusion,
   - ❖ frequency
   - ❖ calculation of the transfusion index in packed RBCs ml/Kg/year.

c. Chelation history:

   - ❖ drug taken,
   - ❖ dose.

d. History of haemolytic crisis.

e. Past history of splenectomy, viral hepatitis (type and date of diagnosis).

f. Family history of anaemia.

g. Symptoms of cardiac affection (palpitation or dyspnea).

h. History of renal or hepatic affection.

i. Full neurological data (sheet in the appendix).

B. Examination:

Thorough clinical examination with particular emphasis on:

a. Anthropometric measures:

- ❖ weight in kilograms
- ❖ height in centimetres.

And the values were plotted against Egyptian percentiles for age and sex.

b. Tanner staging for sexual maturity rating.

c. Complexion and signs of vitality (pallor, jaundice).

d. Chest , heart and abdominal examination for organomegaly.

e. Full neurological examination (sheet in the appendix).

C. Investigations included:

Laboratory investigations:

-Complete blood count using Coulter GEN-S device and the mean pretansfusion haemoglobin over the last year prior to the study was calculated.

-Hemoglobin electrophoresis (using Variant Bio Rad device and high performance liquid chromatography technique) at time of diagnosis and at the onset of the study and the mean hemoglobin F was calculated.

-Liver function tests.

-Renal function tests.

-Serum iron and ferritin (normal=10 to 200 µg/L). (Morrison E D et al.,2003)

Radiological investigations:

- **Computed Tomography :**

CT scan on dorsal and lumbosacral region (D10-L2) was performed to all groups of patients.

Device used: CT Prospeed Vx 2861

Position: supine

Head first

Slice interval : 3mm

Slice thickness: 3mm

KV: 140

mAm: 100

field of vision: 12-15

matrix size: 256x256

filming: soft with window width and window level 250, 50 reciprocal

bone with window width and window level 1500, 250 reciprocal.

- **Magnetic Resonance Imaging ;**

MRI was done to patients suspected to have EMH by clinical examination and by CT.

Device: G.E. contour, 0.5 Tesla
Phased array coil
Sagittal T2 and T1 weight images for the dorsolumbar region (D8-sacrum)
Axial cuts for areas showing evidence of EMH

Data management:

Data were collected, revised, verified then edited on personal computer. Data were then analysed statistically using SPSS statistical package version 3.

The following tests were done:

1. $\bar{X}$=mean
2. SD=standard deviation
3. T test for independent samples
4. ANOVA= analysis of variance
5. X^2=Chy square test

Results

The results of the present study are listed in tables (6 - 25) and figures (17 - 28).

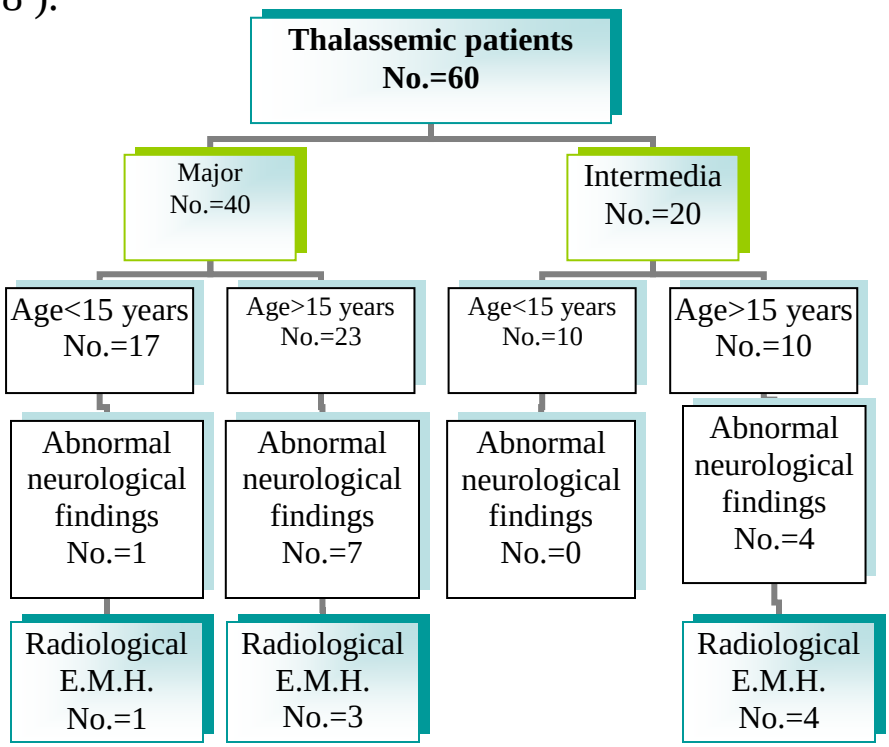


Fig. (17) E.M.H. diagnosis among thalassemic patients suspected clinically and confirmed by CT and MRI.

Fig. (17) demonstrates that of the 60 thalassemic patients 40 patients had thalassemia major , 17 of them were aged less than 15 years old. One patient of this group was confirmed to have EMH and in the rest 23 patients aged more than 15 years old, 3 of them were confirmed to have EMH.

In the 20 patients having thalassemia intermedia, 10 of them were aged less than 15 years old, no one of this group had EMH. The rest 10 patients aged more than 15 years old, 4 of them had EMH.

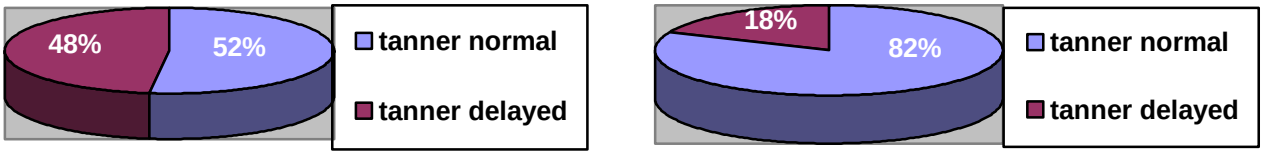
Tab.(6) clinical & demographic data of the studied groups of thalassemic patients..

	Major No.=40		Intermedia No.=20		X^2value	P value
	No.	%	No.	%		
Sex	♂ 24 ♀ 16	60% 40%	8 12	40% 60%	2.1	>0.05 N.S.
Positive Consanguinity	24	60%	7	35%	3.3	>0.05 N.S.
Positive F.H. of anaemia	19	47.5%	3	15%	6.5	<0.01 H.S.
Positive Splenectomy	32	80%	6	30%	14.3	<0.01 H.S.
Positive P.H. of Heart failure	4	10%	none	0 %	2.1	>0.05 N.S.
Positive H. of viral hepatitis	14	35%	4	20%	1.4	>0.05 N.S.
Age in years (mean ± SD)	15 ± 5.3		13 ± 4.6		1.5	>0.05 N.S.
Age of first transfusion in years (mean ± SD)	0.8 ± 0.6		7.3 ± 3		12.8	<0.01 H.S.

Table (6) shows that there was a non significant difference between the two thalassemic groups as regard sex, age, consanguinity, cardiac and hepatic affection, although there was a highly significant difference between the two groups as regards family history of anaemia, splenectomy and age of first blood transfusion.

Tab. (7) anthropometric measures & pubertal staging for the studied groups of thalassemic patients:-

Variable		Major		Intermedia		X^2 value	P value
		No.	%	No.	%		
Weight for age **(Egyptian percentile curves)**	>10th Perc. <10th Perc.	32 8	80% 20%	18 2	90% 10%	0.96	>0.05 N.S.
Height for age **(Egyptian percentile curves)**	>10th Perc. <10th Perc.	27 13	67.5% 32.5%	17 3	85% 15%	2.9	>0.05 N.S.
Tanner stage **(Tanner & white house)**	Normal Delayed	13 12	52% 48%	9 2	81.8% 18.2%	6.5	<0.01 H.S.
Prepubertal		15		9			



Thalassemia major **Thalassemia intermedia**

Fig. (18) showing pie representation of tanner staging in both types of thalassemia.

This table shows that higher percentage of thalassemia major patients were below tenth percentile for weight and height when compared to thalassemia intermedia, although this difference did not reach a statistically significant level. While there was a highly significant difference between the two groups regarding delayed puberty.

Tab. (8) blood transfusion & chelation therapy for the studied groups of thalassemic patients:-

Variable		Major		Intermedia		X^2 value	P value
		No.	%	No.	%		
Frequency of transfusion	>1/ month	31	77.5%	none	none	34.8	<0.01 H.S.
	≤1/month	9	22.5%	12	60%		
	none transfused	0	0%	8	40%		
Chelation type	Desferral	32	80%	14	100%	2.8	>0.05 N.S.
	Oral chelators	8	20%	0	0%		
Chelation dose	Adequate	32	80%	10	50%	0.9	>0.05 N.S.
	Inadequate	8	20%	4	20%		
	Non chelated	0	0%	6	30%		

Table (8) shows a non significant difference between the two groups as regards type of chelation and chelation dose, while there was a highly significant difference between the two groups regarding frequency of transfusion (N.B. adequate chelation >60% of the prescribed weekly dose, inadequate chelation ≤ 60% of the prescribed weekly dose).

Tab. (9) main Laboratory differences between the two studied groups of thalassemic patients:

		Range	Mean	S.D.	T value	Sig.
Hb F (%) at diagnosis	Major Intermedia	36-60 24-6	49.2 16	±7 ±5	17	<0.01 H.S.
Mean pretransfusion Hblevel in last year(mg/dl)	Major Intermedia	6-7.9 5.5-10	6.8 7.6	±0.5 ±1.9	-2.6	<0.01 H.S.
Mean S. Ferritin in last year(µg/ml)	Major Intermedia	1600-3000 200-1550	2075 810	±888 ±523	5.3	<0.01 H.S.

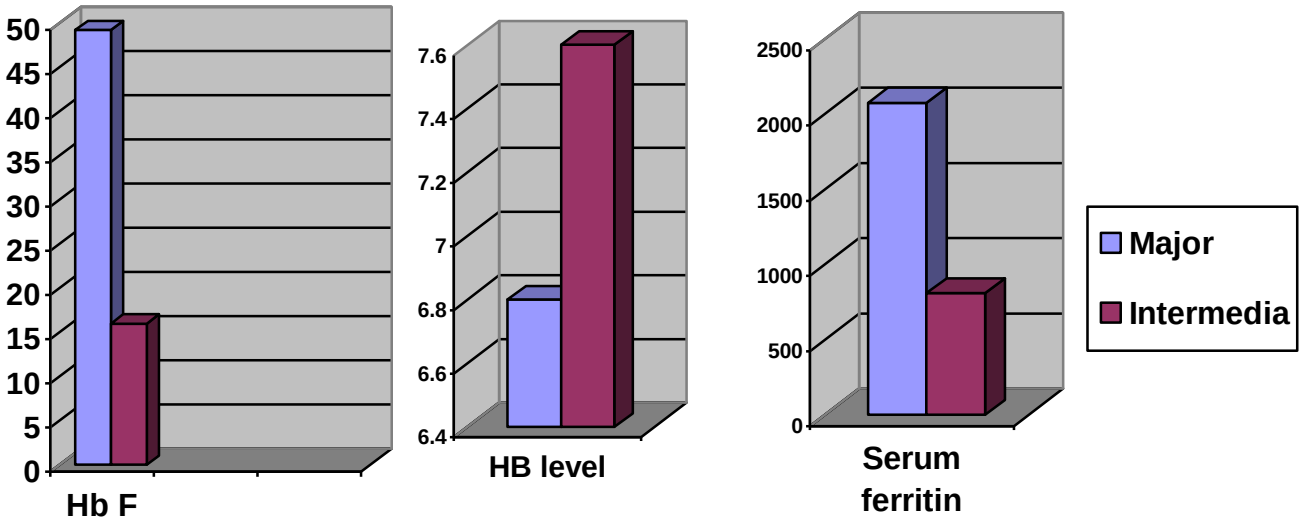


fig.(19) shows difference between both types of thalassemia regarding main laboratory parameters.

This table shows a highly significant difference between the two groups as regards mean pretransfusion Hb. in last year, mean Hb. F at diagnosis and mean serum ferritin in last year.

Table (10) neurological and radiological findings of the studied thalassemic patients:

			Group 1 No.=17		Group 2 No.=23		Group 3 No.=10		Group 4 No.=10		X^2 value	P value
			No.	%	No.	%	No.	%	No.	%		
Neurological findings		Abn.	1	5.9%	7	28.1%	0	0%	4	40%	8	<0.05 S.
		Norm.	16	94.1%	16	71.9%	10	100%	6	60%		
Radiological findings (CT&MRI)	Trabec-ulations	↓ N.	4	23.5%	19	82.6%			5	50%	24.3	<0.01 H.S.
			13	76.5%	4	17.4%	10	100%	5	50%		
	Soft T. Density	↑	1	5.9%	3	13%			4	40%	8.5	<0.05 S.
		N.	16	94.1%	20	87%	10	100%	6	60%		

This table shows that 40 % of group 4 (thalassemia intermedia > 15 years old) had positive neurological findings compared to 28.1% and 5.9% in group 2 and 1 respectively and this difference was statistical significant, also a significant difference between the four groups regarding soft tissue density with higher percentage (40%) in group 4 (thalassemia intermedia > 15 years old).

There is a highly significant difference between the four groups regarding decreased trabeculations -i.e. indicating osteopenia- (82.6% of β thalassemia major patients aged more than 15 years old had decreased trabeculations).

Tab (11) Relation between chelation adequacy versus neurological and radiological findings in the thalassemic patients:-

Variable			No.	%	X^2	Sig.
Normal neurological findings		Adequate	39	92.9%	24.4	<0.01 H.S.
		Inadequate	3	7.1%		
Abn. neurological findings		Adequate	2	66.6%		
		Inadequate	10	83.4%		
Radiological	**Trabeculations N.**	Adequate	18	69.2%	4.2	>0.05 N.S.
		Inadequate	8	30.8%		
	Trabeculations ↓	Adequate	11	69.3%		
		Inadequate	17	60.7%		
	Soft T Density N.	Adequate	40	86.9%	22	<0.01 H.S.
		Inadequate	6	13.1%		
	Soft T Density ↑	Adequate	1	12.5%		
		Inadequate	7	87.5%		

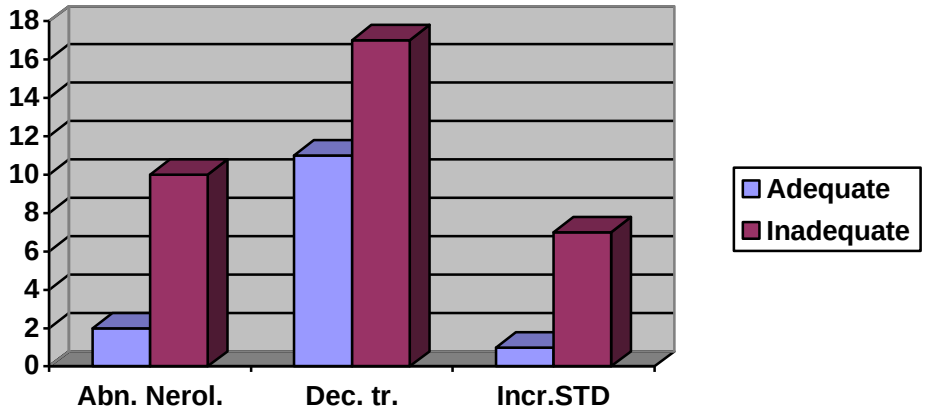


Fig.(20) shows relation between chelation adequacy versus abnormal neurological and radiological findings.

Table (11) shows that neurological findings and soft tissue density were highly related to inadequate chelation therapy, while there was a non significant relation between decreased trabeculations and inadequate chelation.(N.B. number of chelated patients was 54 patients, adequate chelation >60% of the prescribed weekly dose, inadequate chelation ≤ 60% of the prescribed weekly dose)

Tab (12) Relation between chelation adequacy versus neurological and radiological findings in β thalassemia major patients>15 years old:-

Variable		*β Thalassemia major ›15 No=23*			
		No.	%	X^2	Sig.
Normal Neurological findings	Adequate	14	88.2%	15.2	<0.01 H.S.
	Inadequate	2	11.8%		
Abn. Neurological findings	Adequate	0			
	Inadequate	7	100%		
Trabeculations N	Adequate	4	100%	2.5	>0.05 N.S.
	Inadequate	0			
Trabeculations↓	Adequate	8	42.1%		
	Inadequate	11	57.9%		
Soft T density N.	Adequate	15	75%	6.4	<0.05 S.
	Inadequate	5	25%		
Soft T density ↑	**A**dequate	0			
	Inadequate	3	100%		

Tab (13) Relation between chelation adequacy versus neurological and radiological findings in *β Thalassemia Intermedia* patients>15 years old:-

Variable		*β Thalassemia Intermedia ›15 No=10*			
		No.	%	X^2	Sig.
Normal Neurological findings	Adequate	6	100%	8	<0.05 S.
	Inadequate	0			
Abn. Neurological findings	Adequate	0	100%		
	Inadequate	4			
Trabeculations N	Adequate	3	60%	0.55	>0.05 N.S.
	Inadequate	2	40%		
Trabeculations↓	Adequate	2	40%		
	Inadequate	3	60%		
Soft T density N.	Adequate	6	100%	8	<0.05 S.
	Inadequate	0			
Soft T density ↑	Adequate	0	100%		
	Inadequate	4			

Tables (12) and (13) show that the relation between chelation adequacy and neurological findings was highly significant in patients with β thalassemia major ›15 years old & significant in patients with β thalassemia intermedia ›15, while the relation between chelation adequacy & with decreased trabeculations was non significant in both groups & the relation between chelation adequacy with soft tissue density was significant in both groups.

Tab (14) Relation between mean serum ferritin(in µg/ml) versus neurological and radiological findings in the thalassemic patients:

Variable	**mean**	***S.D.***	***T***	***Sig.***
Normal Neurological findings	**1371**	**876**	**-5.3**	**‹0.01 H.S.**
Abn. Neurological findings	**2909**	**831**		
Trabeculations N	**1037**	**773**	**-6.2**	**‹0.01 H.S.**
Trabeculations↓	**2357**	**869**		
Soft T density N.	**1503**	**1013**	**-2.9**	**‹0.05 S.**
Soft T density↑	**2625**	**744**		

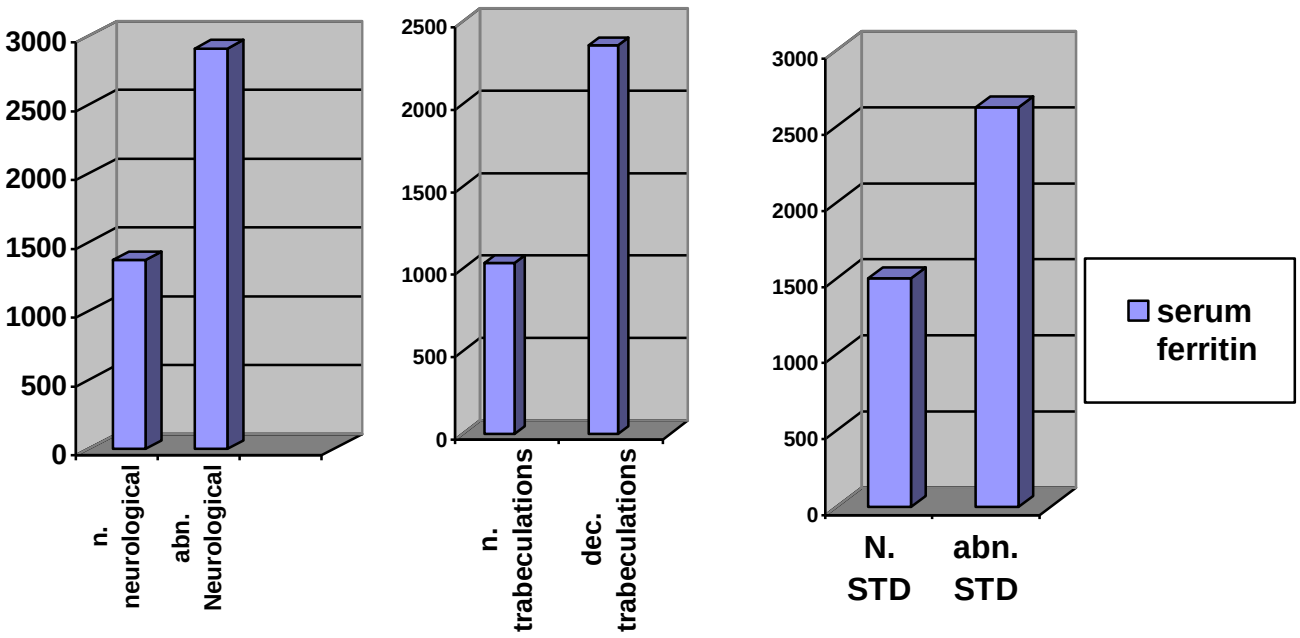


Fig.(21) shows relation between mean serum ferritin versus neurological and radiological findings.

Table (14) shows a highly significant relation between mean serum ferritin with neurological findings and with decreased trabeculations and significant relation was found as regards soft tissue density.

Tab (15) relation between mean serum ferritin (in µg/L) versus neurological and radiological findings in β Thalassemia major patients ›15 years old:-

Variable	β Thalassemia major ›15 ys.(no=23)			
	Mean	***S.D.***	***T***	***Sig***
Normal Neurological findings	*2117*	*696*	*-4.3*	*‹0.01 H.S.*
Abn. Neurological findings	*3500*	*547*		
Trabeculations N	*1500*	*577*	*-2.7*	*‹0.05 S.*
Trabeculations ↓	*2684*	*820*		
Soft T density N.	*2350*	*875*	*-2.8*	*‹0.05 S.*
Soft T density ↑	*3333*	*577*		

Tab (16) relation between mean serum ferritin(in µg/L) versus neurological and radiological findings in β Thalassemia intermedia ›15 years old:-

Variable	β Thalassemia intermedia ›15 ys.(no=10)			
	Mean	***S.D.***	***T***	***Sig***
Normal Neurological findings	*616*	*421*	*-5.5*	*‹0.01 H.S.*
Abn. Neurological findings	*2250*	*500*		
Trabeculations N	*940*	*1199*	*-1.2*	*›0.05 N.S.*
Trabeculations ↓	*1600*	*547*		
Soft T density N.	*616*	*421*	*-5.5*	*‹0.01 H.S.*
Soft T density ↑	*2250*	*500*		

Tables (15) and (16) show a highly significant relation between mean serum ferritin and neurological findings in both groups & the relation between mean serum ferritin and decrease trabeculations was significant in β thalassemia major ›15 years old & non-significant in patients with β thalassemia intermedia ›15 years old, while the relation between mean serum ferritin & soft tissue density was significant in patients with β thalassemia major ›15 years old & highly significant in patients with β thalassemia intermedia ›15 years old.

Tab. (17) relation between transfusion frequency per month versus neurological and radiological findings in all the thalassemic patients:-

Variable	No.	Mean	S.D.	T	Sig
Normal Neurological findings	40	1.6	±0.6	-2.2	<0.05 S
Abn. Neurological findings	12	0.7	±0.3		
Trabeculations N.	24	1	±0.4	0.2	>0.05 N. S
Trabeculations↓	28	0.8	±0.3		
Soft T.D. N.	44	1.1	±0.4	-2.7	<0.05 S
Soft T.D.↑	8	0.6	±0.2		

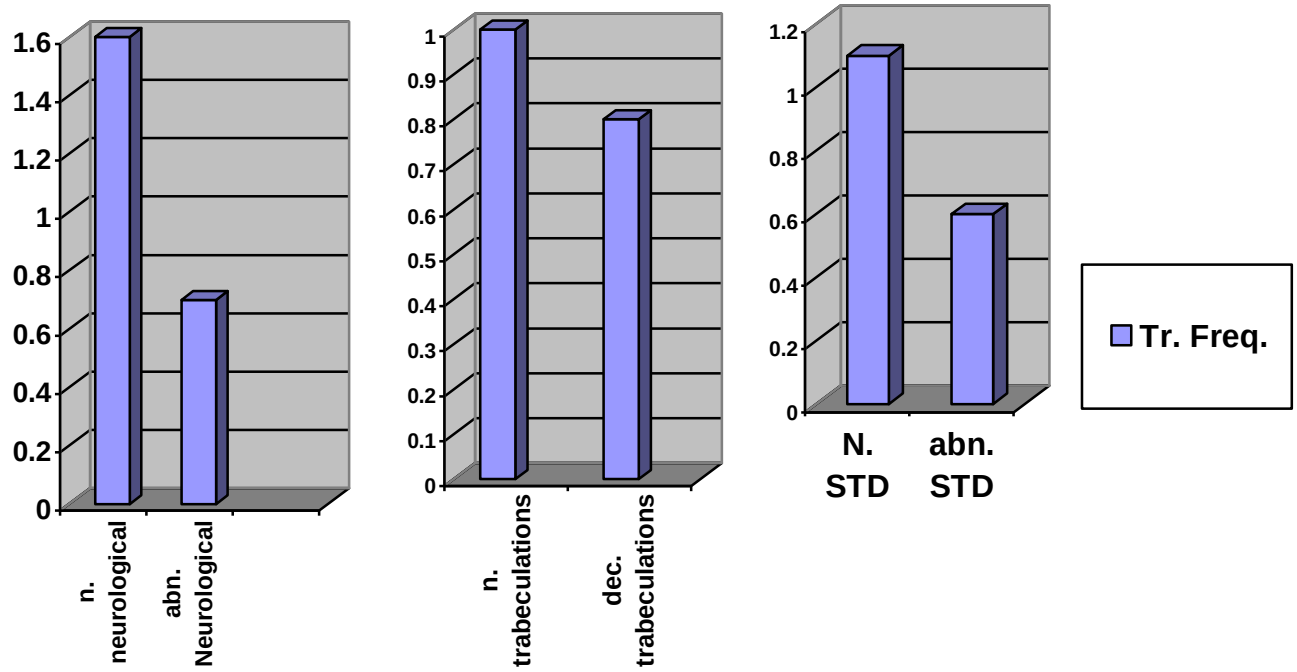


Fig.(22) shows relation between transfusion frequency versus neurological and radiological findings.

This table shows that there is a significant relation between transfusion frequency with both neurological findings and soft tissue density, while there is a non significant relation between transfusion frequency with decreased trabeculations.(N.B. number of transfused thalassemic patients = 52 patients).

Tab. (18) relation between transfusion frequency per month versus neurological and radiological findings in β thalassemia major patients > 15 years old:-

Variable	β thalassemia major(no=23)				
	No.	Mean in times	S.D.	T	Sig
Normal Neurological findings	16	1.8	±0.6	-5.2	<0.01 HS
Abn. Neurological findings	7	0.9	±0.3		
Trabeculations N.	4	2	±0.4	-3.7	<0.01 H S
Trabeculations↓	19	1.3	±0.2		
Soft T.D. N.	20	1.6	±0.5	-4.6	<0.01 H S
Soft T.D.↑	3	0.8	±0.3		

Tab. (19) relation between transfusion frequency per month versus neurological and radiological findings in β thalassemia intermedia patients > 15 years old:-

Variable	β thalassemia intermedia(no=10)				
	No.	Mean in times	S.D.	T	Sig
Normal Neurological findings	6	0.5	±0.2	-2.7	<0.05 S
Abn. Neurological findings	4	0.2	±0.1		
Trabeculations N.	5	0.6	±0.2	0.6	>0.05 NS
Trabeculations↓	5	0.5	±0.2		
Soft T.D. N.	6	0.7	±0.3	-1.7	>0.05 NS
Soft T.D.↑	4	0.4	±0.1		

Tables (18) and (19) show the relation between transfusion frequency with neurological findings, decreased trabeculations and soft tissue density which were highly significant in β thalassemia major patients aged more than 15 years old, while the relation between transfusion frequency and neurological findings was significant in β thalassemia intermedia patients aged more than 15 years old, and the relation between transfusion frequency with decreased trabeculations and soft tissue density was non significant in β thalassemia intermedia patients aged more than 15 years old.

Tab. (20) relation between mean pretransfusion Hb. level versus neurological and radiological findings in all the thalassemic patients:-

Variable	No.	Mean in gm/dl	S.D.	T	Sig
Normal Neurological findings	41	7.3	±0.8	3.76	<0.01 HS
Abn. Neurological findings	11	5.9	±2		
Trabeculations N.	24	7.5	±0.9	3.14	<0.01 HS
Trabeculations↓	28	6.5	±1.3		
Soft T.D. N.	44	7.2	±0.8	-3	<0.01 HS
Soft T.D.↑	8	5.8	±2.4		

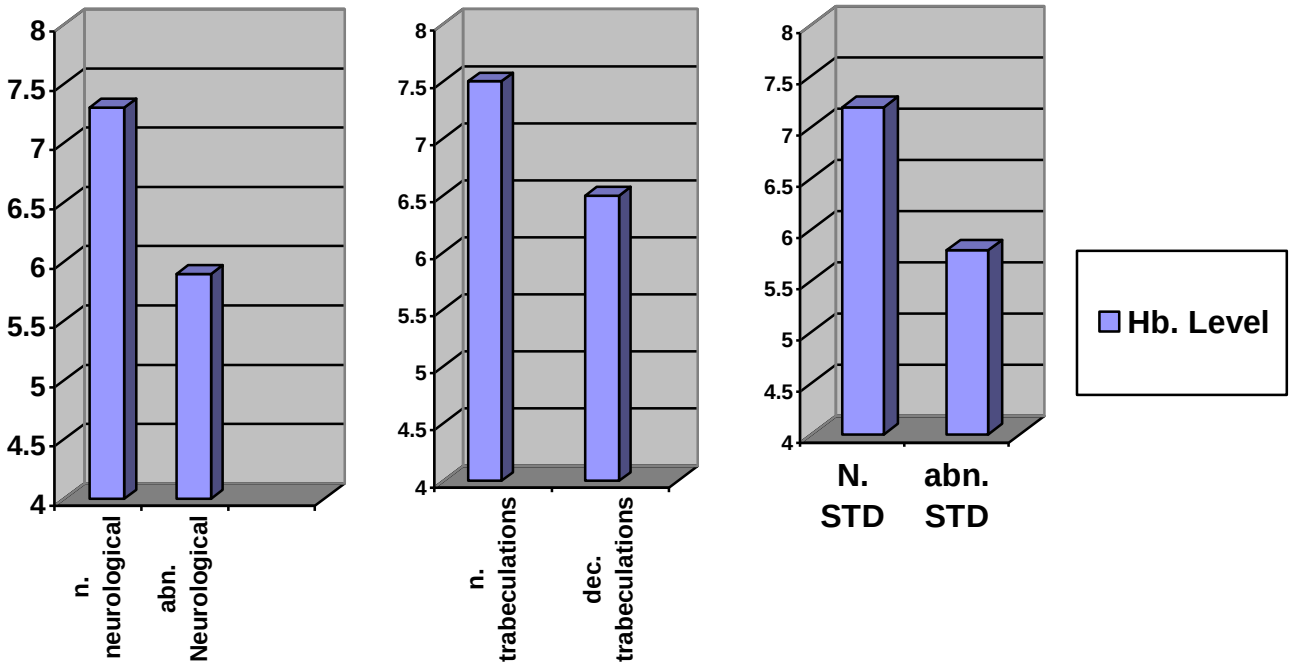


fig.(23) shows relation between mean pretransfusion Hb. Level versus neurological and radiological findings

Table (20) shows a highly significant relation between mean Hb. with neurological findings, decreased trabeculations and soft tissue density.

Tab. (21) relation between mean pretransfusion Hb. level versus neurological and radiological findings in β thalassemia major patients > 15 years old:-

Variable	β thalassemia major (no=23)				
	No.	Mean	S.D.	T	Sig
Normal Neurological findings	16	7	±0.3	4.7	<0.01 HS
Abn. Neurological findings	7	6.2	±0.4		
Trabeculations N.	4	7.2	±0.5	2.8	<0.05 S
Trabeculations ↓	19	6.6	±0.2		
Soft T.D. N.	20	6.9	±0.4	2.6	<0.05 S
Soft T.D.↑	3	6.1	±0.5		

Tab. (22) relation between mean pretransfusion Hb. level versus neurological and radiological findings in β thalassemia intermedia patients > 15 years old:-

Variable	β thalassemia intermedia (no=10)				
	No.	Mean	S.D.	T	Sig
Normal Neurological findings	6	8.1	±0.7	3	<0.05 S
Abn. Neurological findings	4	5.2	±1.5		
Trabeculations N.	5	8.2	±0.8	2.5	<0.05 S
Trabeculations ↓	5	5.8	±2.2		
Soft T.D. N.	6	8.1	±0.7	2.7	<0.05 S
Soft T.D.↑	4	5.2	±1.5		

Tables (21) and (22) show highly significant relation between mean Hb level with neurological findings in β thalassemia major patients aged more than 15 years old and significant in β thalassemia intermedia patients aged more than 15 years old.

It also shows that the relation between mean Hb level with decreased trabeculations and with soft tissue density was significant in both β thalassemia major and β thalassemia intermedia patients aged more than 15 years old.

Tab.(23) relation between transfusion index(in ml/Kg/year) versus neurological and radiological findings in all the thalassemic patients:

Variable	No.	Mean in ml/Kg/year	S.D.	T	Sig
Normal Neurological findings	41	130	±35	5.45	<0.01 HS
Abn. Neurological findings	11	80	±25		
Trabeculations N.	24	117	±23	1.46	>0.05 NS
Trabeculations↓	28	95	±27		
Soft T.D. N.	44	120	±31	4.7	<0.01 HS
Soft T.D.↑	8	83	±20		

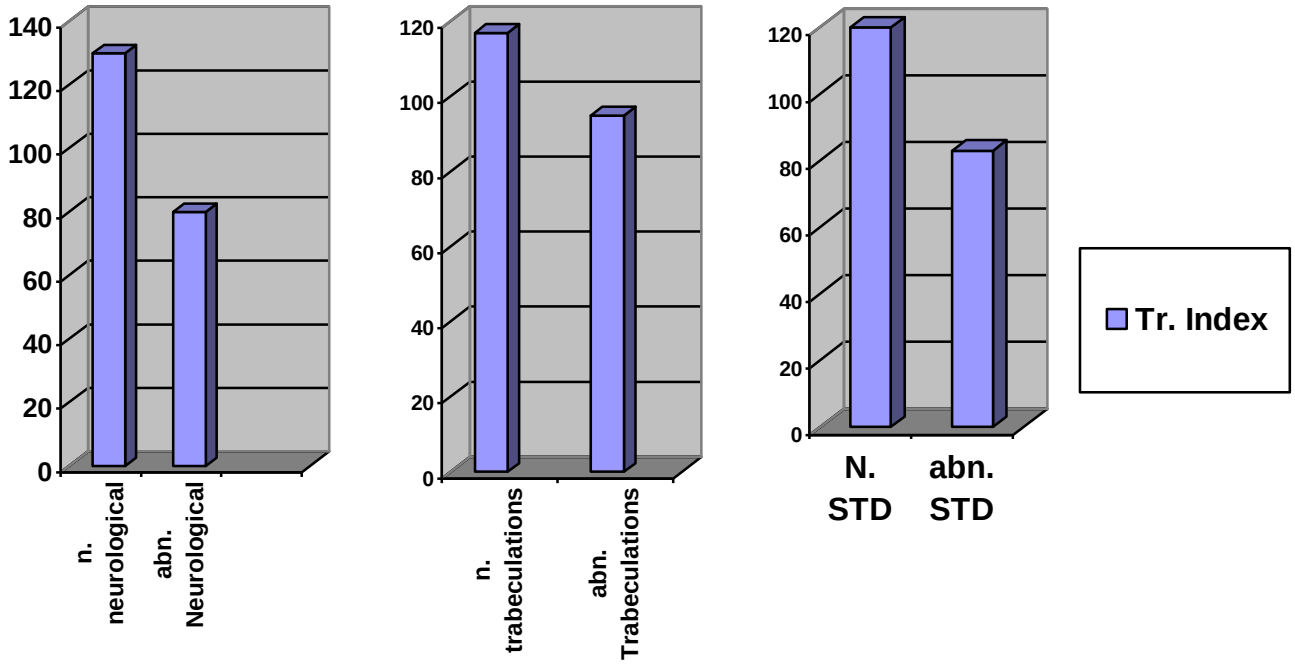


fig.(24) shows relation between transfusion index versus neurological and radiological findings.

This table shows a highly significant relation between transfusion index with neurological findings and soft tissue density while there was a non significant relation between transfusion index and decreased trabeculations.

Tab.(24) relation between transfusion index(in ml/Kg/year) versus neurological and radiological findings in β thalassemia major patients >15 years old :

Variable	β thalassemia major (no=23)				
	No.	Mean	S.D.	T	Sig
Normal Neurological findings	16	150	±37	5.8	<0.01 HS
Abn. Neurological findings	7	85	±22		
Trabeculations N.	4	136	±25	2.6	<0.05 S
Trabeculations ↓	19	95	±20		
Soft T.D. N.	20	133	±27	4.7	<0.01 HS
Soft T.D.↑	3	70	±24		

Tab.(25) relation between transfusion index(in ml/Kg/year) versus neurological and radiological findings in β thalassemia intermedia patients >15 years old :

Variable	β thalassemia intermedia (no=10)				
	No.	Mean	S.D.	T	Sig
Normal Neurological findings	6	124	±27	2.6	<0.05 S
Abn. Neurological findings	4	90	±20		
Trabeculations N.	5	120	±23	1.8	>0.05 NS
Trabeculations ↓	5	95	±17		
Soft T.D. N.	6	117	±22	1.4	>0.05 NS
Soft T.D.↑	4	98	±15		

Tables (24) and (25) show a highly significant relation between transfusion index with neurological findings in β thalassemia major patients aged more than 15 years old while this relation was significant in β thalassemia intermedia patients aged more than 15 years old, it also showed significant relation between transfusion index and decreased trabeculations and a highly significant relation between transfusion index and soft tissue density in β thalassemia major patients aged more than 15 years old while these relations were non significant in β thalassemia intermedia patients aged more than 15 years old.

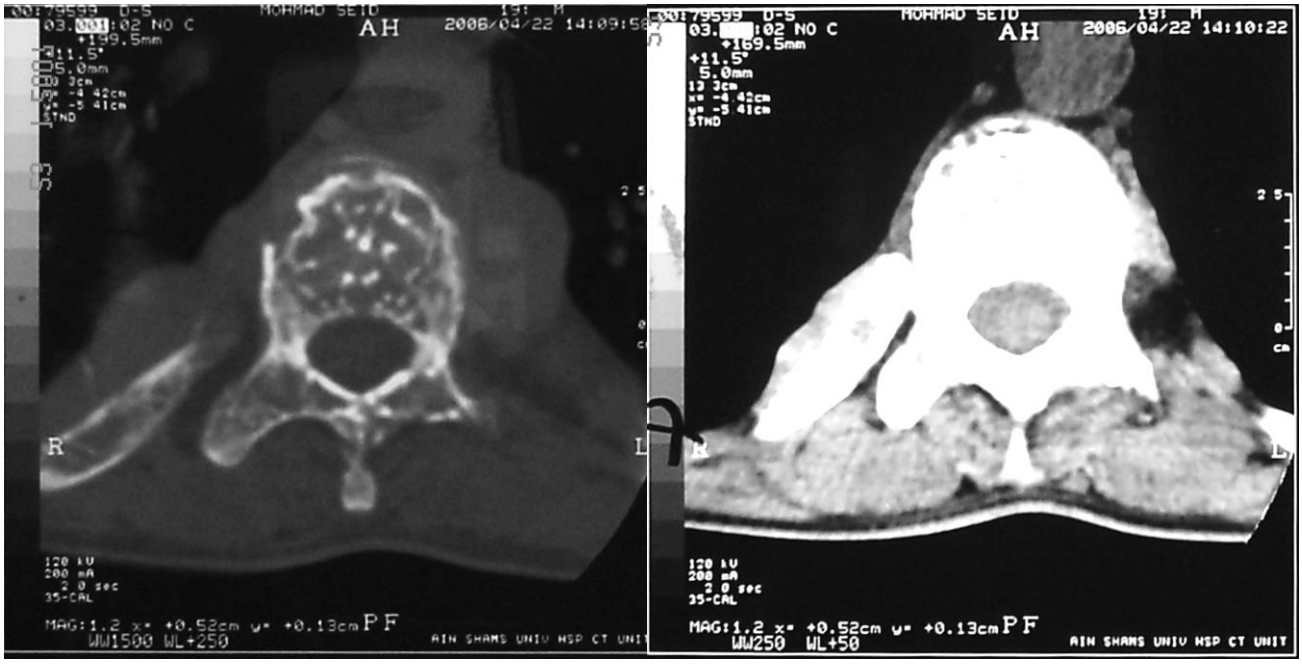


Fig.(25) shows CT scan of dorsal spine for a patient with EMH

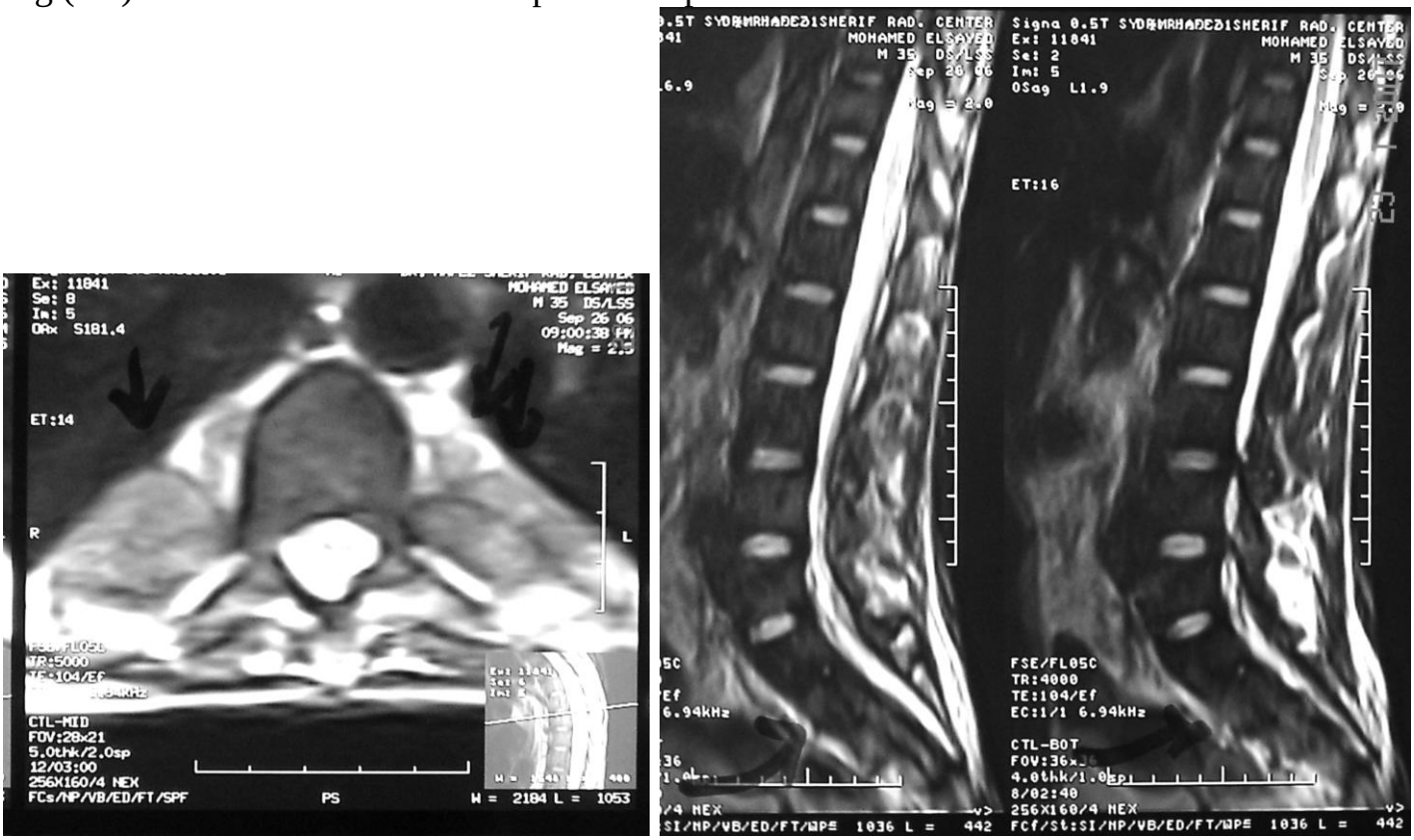


Fig.(26) shows MRI Lumbar spine of the same patient with EMH

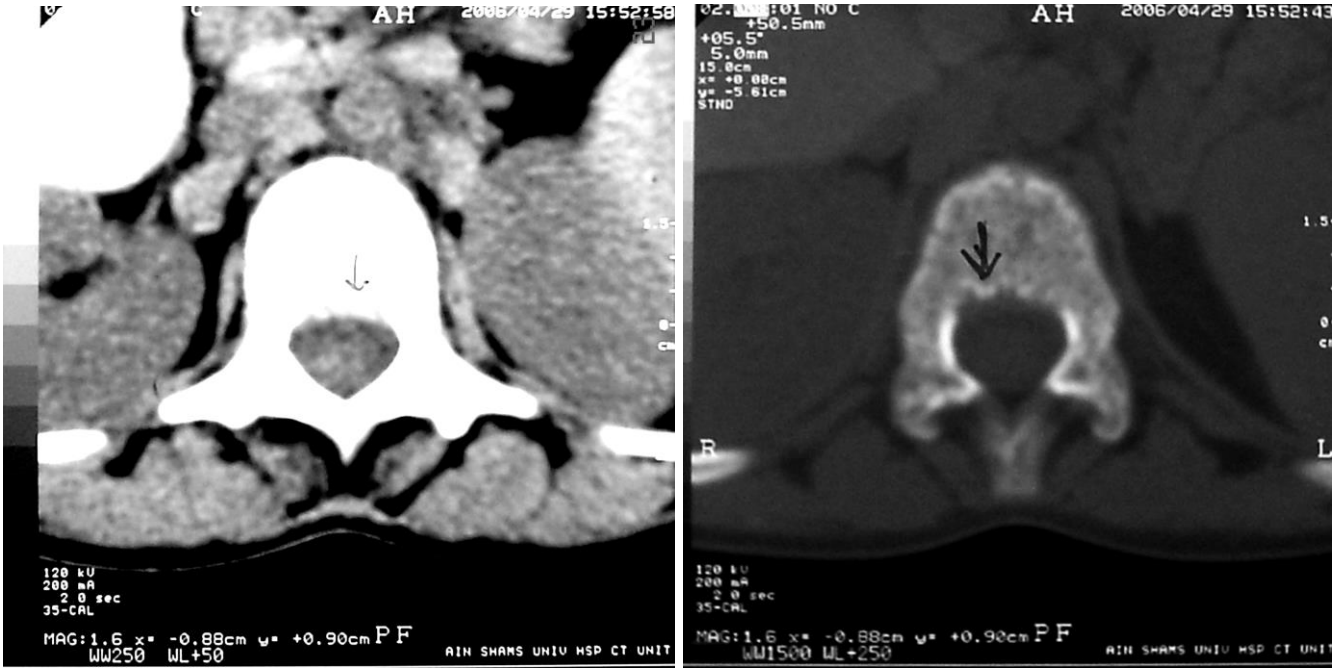
A24-year-old male diagnosed with thalassemia major since the age of one year. He receives packed RBCs of 500cc every month and on chelation by dessferal pump 4 days per weaksince the age of 15 years old. His past medical history revealed splenectomy at the age of 7 years, on examination he was pale. The liver was enlarged 4 cm below the rib edge. It was hard on palpation. The patient complained of back pain and numbness at both lower limbs at the past two years.

On neurological examination there was mild spasticity mainly distally in the flexor group of both lower limbs. Muscle power examination revealed mild to moderate weakness of both lower limbs mainly distally more at the extensors. Deep tendon reflexes were normal except for bilateral exaggerated ankle reflex. Superficial reflexes were normal. There was mild decreased in sensation of both lower limbs till the level of umbilicus when compared to upper limbs and trunk.

On laboratory examination, his hemoglobin level was 6.5 g/dl, hematocrit 22.3 %, erythrocyte count 2,960,000 MCV 70.0 fl, MCHb 20.8 pg. MCHC 24.0 g/dl, leukocyte 4680/mm (PMNL 45.2%, lymphocyte 48.4%, monocyte 6.4%) and his platelet count was 375.000/mm. Blood biochemistry revealed AST 63 IU/L, ALT 61 IU/L, total bilirubin 1.98 mg/dl. and direct bilirubin 0.4 mg/dl, while kidney function tests were normal. His hemoglobin electrophoresis, HbA: 62.0%, HbF 34.4% and HbA_2 3.6%. Mean serum ferritin in the last year was 2600 μg/L.

On CT there was obvious honey combing of the vertebrae denoting marked osteoporosis, it shows also thickening of the transverse process and intermedia tissue density paravertebral, prevertebral and along the ribs.

MRI confirmed the presence of EMH in the paravertebral and prevertebral spaces in the region of T8-L1 vertebrae.



Fig(27) shows CT scan for a patient with EMH

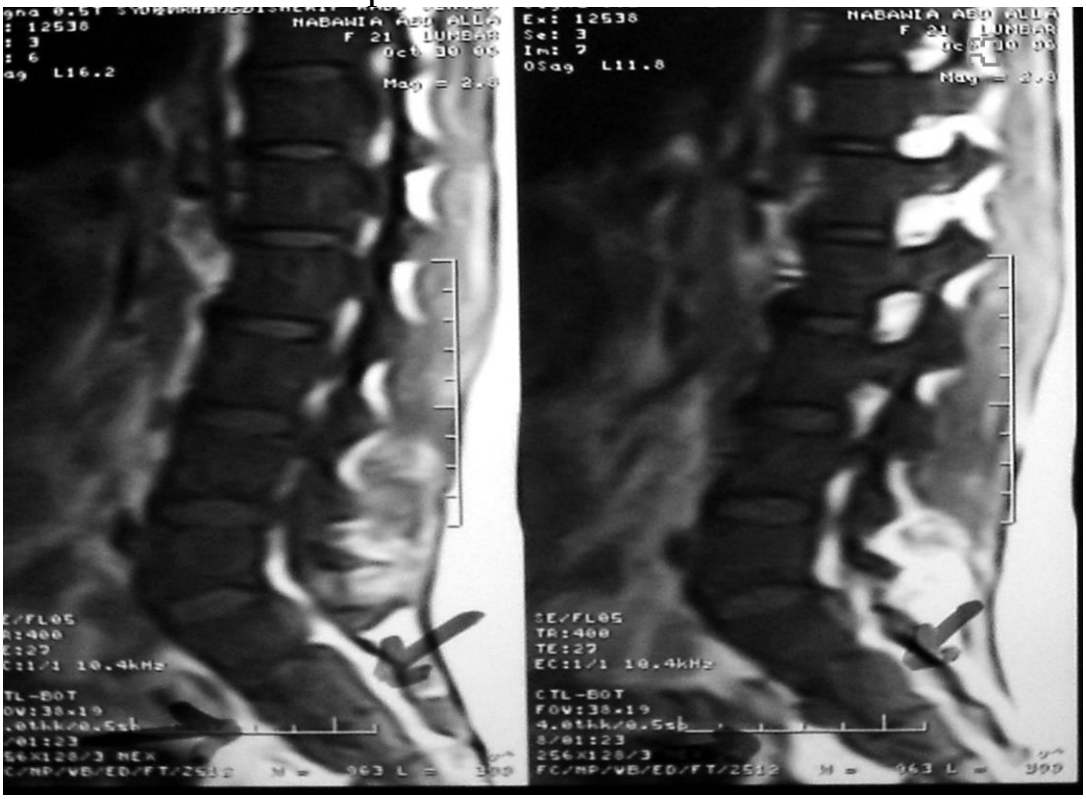


Fig.(28) shows MRI of the same patient with EMH

A 21-year-old female diagnosed with thalassemia intermedia since the age of 3 years. She receives regular packed RBCs of 500cc every 2 months and on chelation by dessferal pump for 3 days per weak since the age of 15 years old. Her past medical history revealed that she did not under gone splenectomy. The liver was enlarged 5 cm below the rib edge. It was hard on palpation. The patient complained of back pain and numbness at both lower limbs at the past year.

On neurological examination there was wasting of muscles of both lower limbs bilateral and symmetrical together with mild spasticity mainly distally in the flexor group. Muscle power examination revealed moderate weakness of both lower limbs mainly distally. Deep tendon reflexes were normal except for bilateral exaggerated ankle reflex. Superficial reflexes were lost at the umbilicus with positive Babiniski sign. There was bilateral and symmetrical decreased sensation of both lower limbs.

On laboratory examination, her hemoglobin level was 7.5 g/dl, hematocrit 30.3 %, erythrocyte count 3,670,000 MCV 75.0 fl, MCHb 22.8 pg. MCHC 30.0 g/dl, leukocyte 6740/mm and her platelet count was 260.000/mm. Blood biochemistry revealed normal liver and kidney functions. Her hemoglobin electrophoresis, HbA: 83.0%, HbF 15% and HbA_2 2%. Mean serum ferritin was 2200 μg/L in the last year.

On CT there was honey combing of the vertebrae denoting moderate osteoporosis.

MRI shows low signals on T2 weighted images, associated EMH at sacral region, mainly at the presacral space and at sacral spinal canal in epidural location.

Neurological examination

A. Mental function:

1) State of consciousness.
2) Orientation for time, place and person.
3) Memory.
4) Mood.
5) Intelligence.
6) Behavior.

B. Speech:

1) Aphasia.
2) Dysarthia.

C. Examination of cranial nerves:

1) Olphactory nerve.
2) Optic nerve.
3) Occulomotor nerve.
4) Trocheal nerve.
5) Trigeminal nerve.
6) Abducent nerve.
7) Facial nerve.
8) Vistibulochoclear nerve.
9) Glossopharengeal nerve.
10) Vagus nerve.
11) Accessory nerve.
12) Hypoglossal nerve.

D. Examination of the motor system:

1) Inspection:
- **a.** Atrophy or hypertrophy.
- **b.** Fasciculation or fibrillation.
- **c.** Involuntary movments.
- **d.** Trophic changes.

2) Examination of muscle tone.
3) Examination of muscle power.
4) Examination of reflexes:
- **a.** Deep reflexes.
- **b.** Superficial reflexes.

E. Examination of the sensory system:

1) Superficial sensations.
2) Deep sensations.
3) Cortical sensations.

F. Examination of coordination.

G. Examination of back and spine.

H. Examination of the cranium.

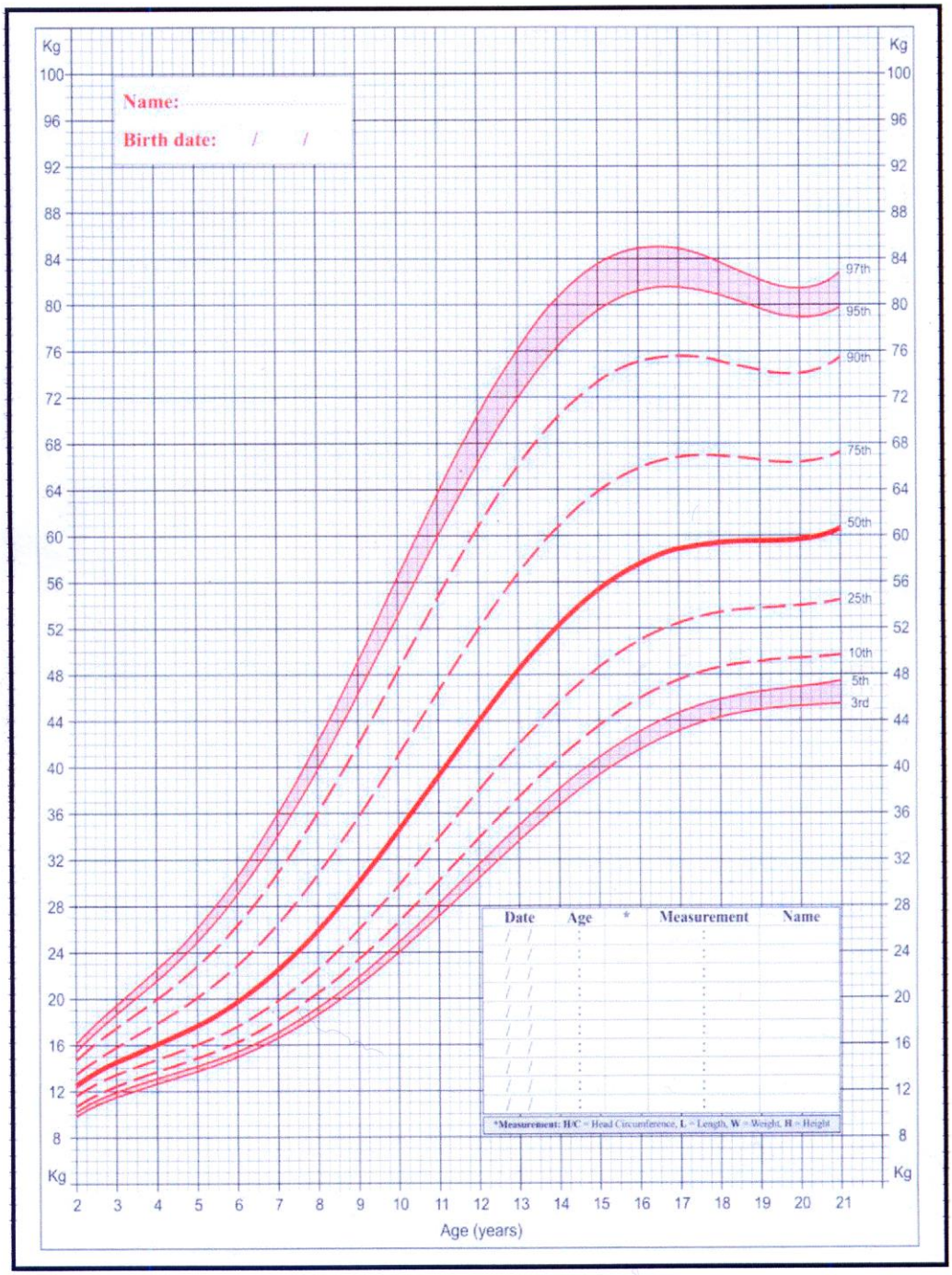
Classification of sexually maturity rating in girls (Tanner's classification) *(Tanner et al., 1976)*.

	Pubic Hair	**Breast**
Stage 1	None	Pre-adolescent
Stage 2	Sparse, lightly pigmented, straight along the medial border of labia.	Breast and papilla elevated as small mound; areolar diameter increased.
Stage 3	The hair is considerably darker, begins to curl, increased amount, sparsely over the junction of the pubis.	Breast and areola enlarged, no contour separation.
Stage 4	Coarse, curly, abundent, but amount less than adult.	Areola and papilla form 2ry mound.
Stage 5	Adult feminine triangle, spread to medial surface of thighs.	Mature, nipple projects, areola part of general breast contour.

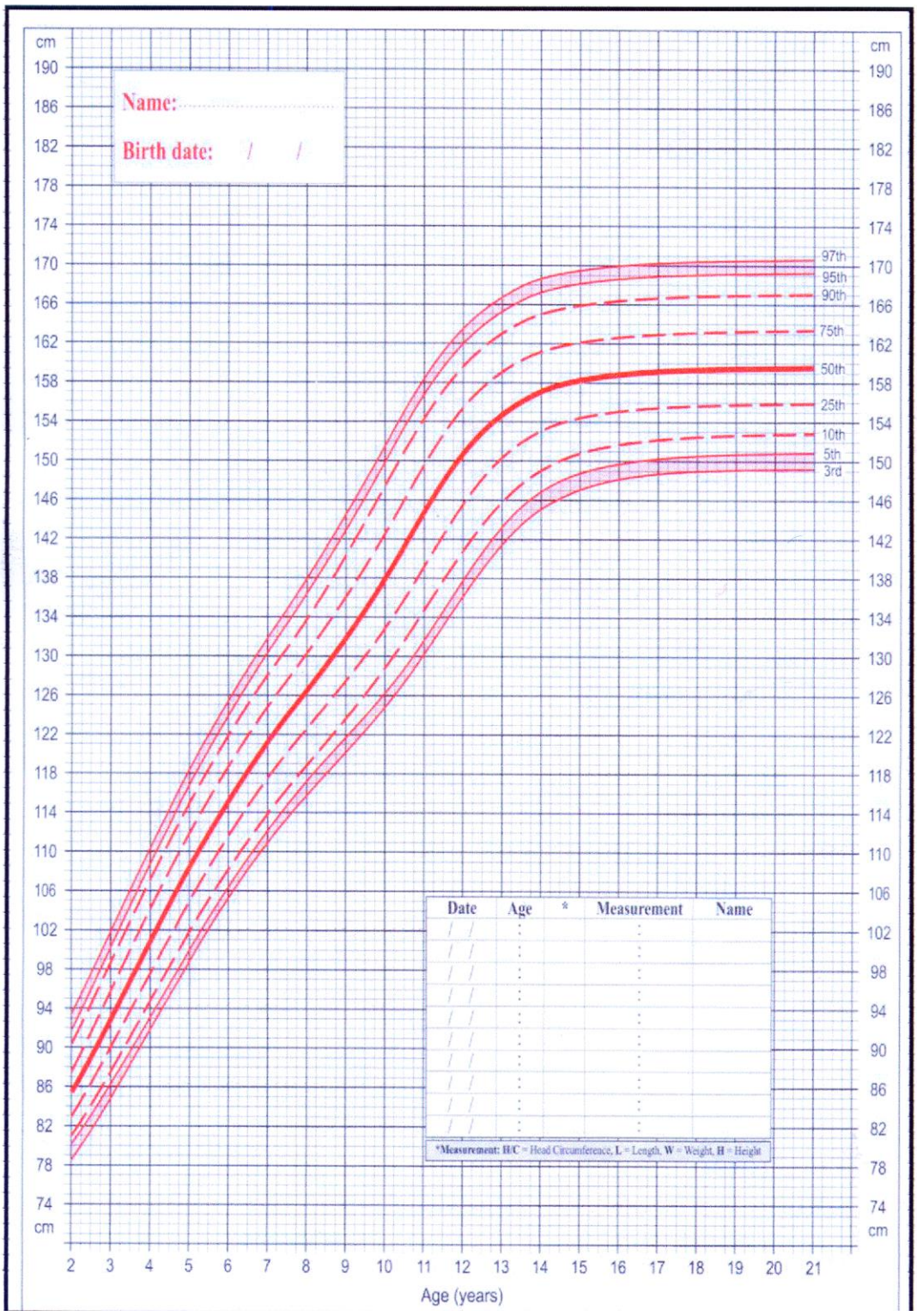
Classification of sexual maturity rating in boys (Tanner's classification) *(Tanner et al., 1976)*.

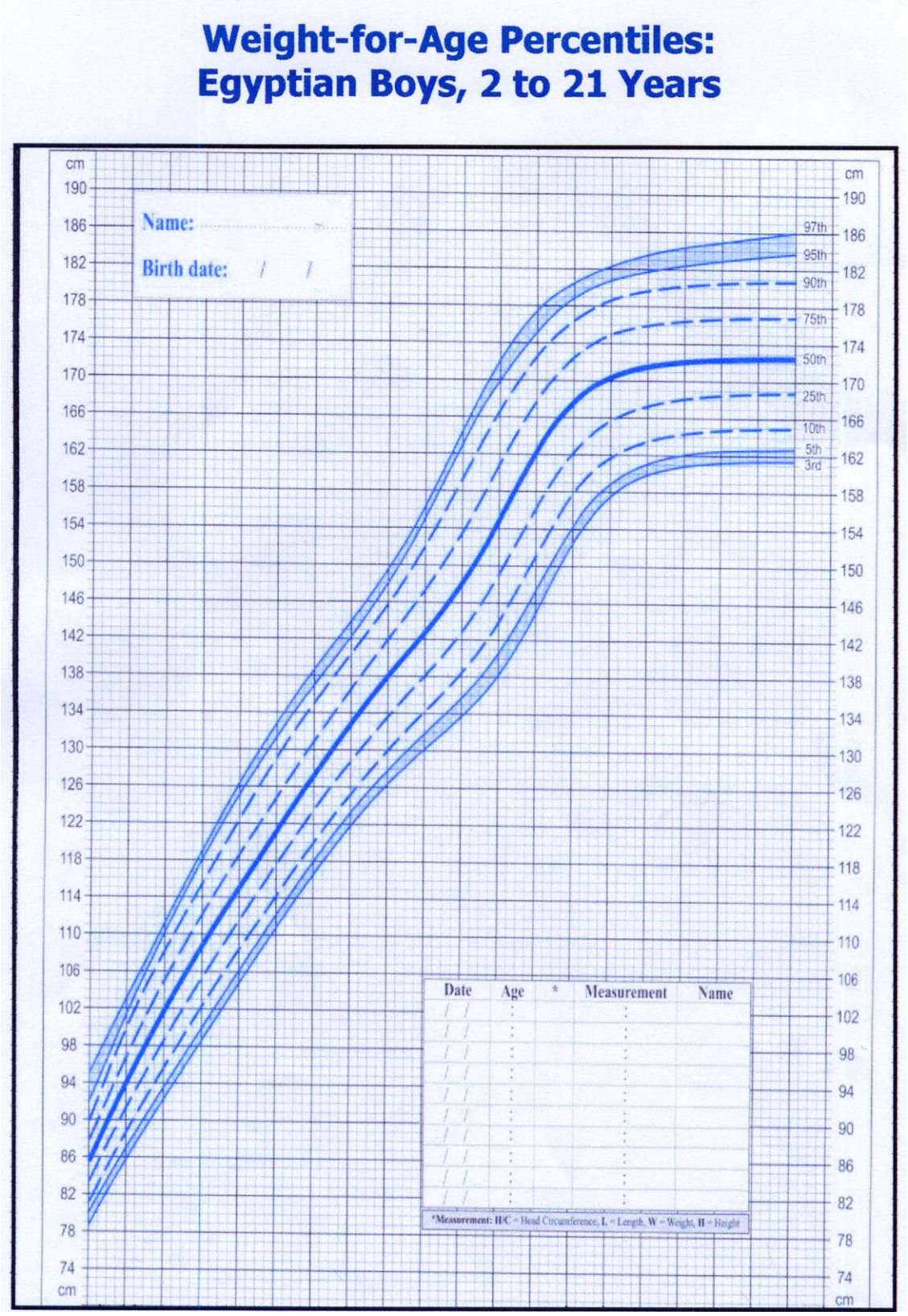
	Pubic Hair	**Penis**	**Testes**
Stage 1	None	Pre-adolescent	Pre-adolescent
Stage 2	The hair is scanty, long, slightly pigmented	Slight enlargement	Enlarged scrotum, pink texture
Stage 3	The hair is considerably darker, starts to curl, but small in amount.	longer	Larger
Stage 4	Resembles adult type, but less in quantity, coarse, curly	Larger, increase in size of glans and breadth	Larger, with dark scrotum
Stage 5	Adult distribution spread to medial surface of thighs	Adult size	Adult size

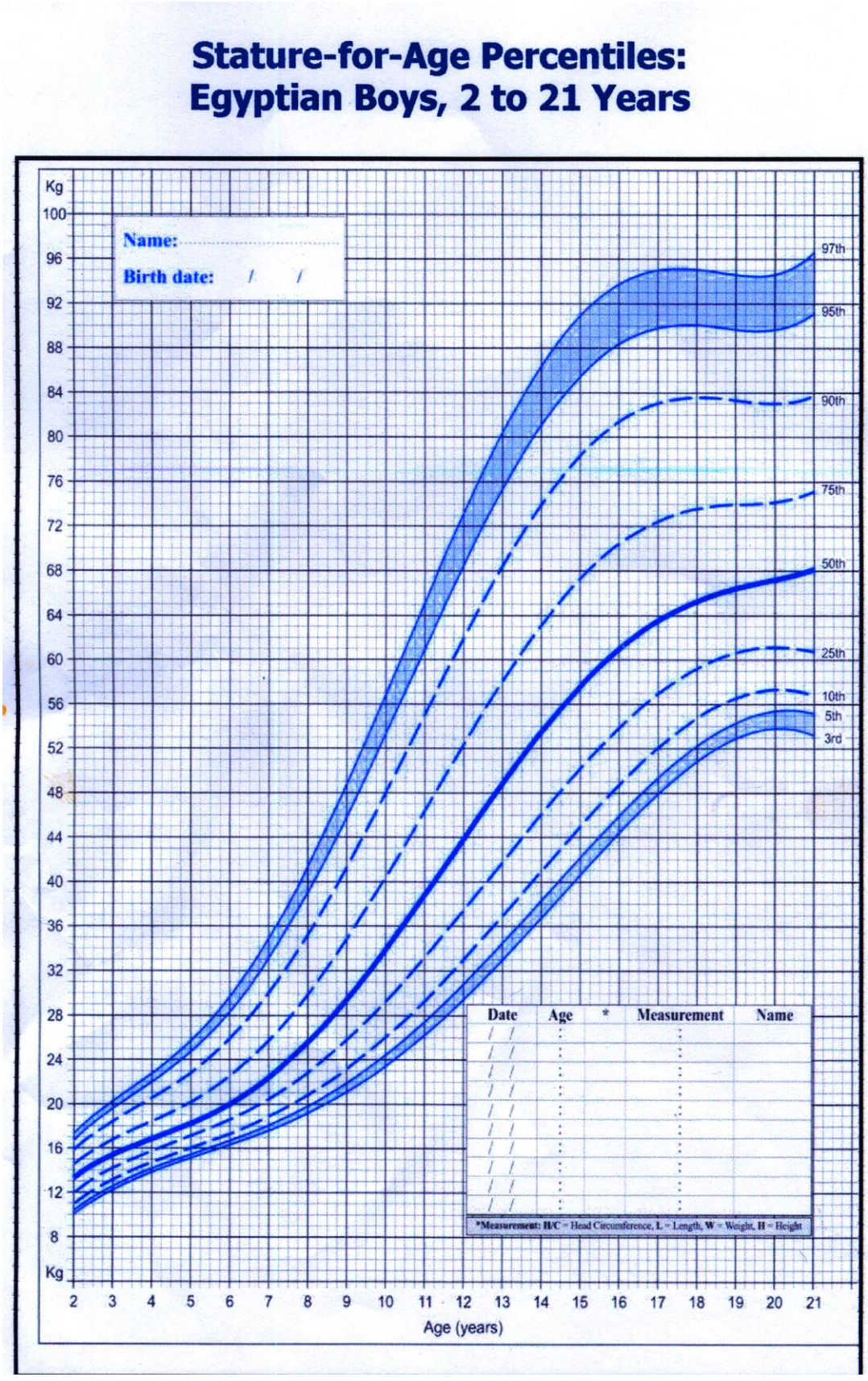
Weight-for-Age Percentiles: Egyptian Girls, 2 to 21 Years



Stature-for-Age Percentiles: Egyptian Girls, 2 to 21 Years




Weight-for-Age Percentiles:
Egyptian Boys, 2 to 21 Years
Name:
Birth date: / /
97th
95th
90th
75th
50th
25th
10th
5th
3rd
cm
Date
Age *
Measurement
Name
*Measurement: H/C = Head Circumference, L = Length, W = Weight, H = Height


Stature-for-Age Percentiles:
Egyptian Boys, 2 to 21 Years
Name:
Birth date: / /
Kg
100
96
92
88
84
80
76
72
68
64
60
56
52
48
44
40
36
32
28
24
20
16
12
8
Kg
97th
95th
90th
75th
50th
25th
10th
5th
3rd
Date
Age
*
Measurement
Name
*Measurement: H/C = Head Circumference, L = Length, W = Weight, H = Height
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
Age (years)

Conclusion

From the previous study, we concluded that EMH is not uncommon as it was thought (present in 13.3% of patients).

It is more common in TI patients (20% in TI patients and 10% in TM patients). It is more likely to be found in elderly patients.

It was found that EMH is related to inadequate chelation and high mean serum ferritin levels and also related to low mean hemoglobin level, decreased transfusion frequency per month and decreased transfusion index.

So we recommend that:

1. Adequate blood transfusion.

2. Insure adequate chelation therapy and monitor the compliance of the patients on this therapy.

3. Regular follow up of both Hb level to be maintained at 9 gm/dL and serum ferritin level to be kept at a safe level.

4. Early initiation of transfusion and iron chelation therapy in TI patients, if there is evidence of growth abnormalities or low hemoglobin level.

5. Thorough neurological examination of the patients specially older age group and TI patients if there is any neurological complain.

6. CT scan should be mandatory for any thalassemic patient with progressive skeletal changes and neurological symptoms for prevention of irreversible neurological damage.

7. MRI if possible to confirm the diagnosis of EMH and the level and extent of the lesion.

8. As osteoporosis was present in a high percent of our patients, calcium supplements should be considered in thalassemic patients.

Discussion

Thalassemia is a hereditary form of anemia resulting from defects in hemoglobin production. Beta thalassemia, a quite common disease in Mediterranean populations, affects multiple organs and is associated with considerable rates of morbidity and mortality. Extramedullary hemopoiesis is a common compensatory phenomenon associated with chronic hemolytic anemia. *(Tsitsopoulos et al., 2007)*

EMH accompanies a wide variety of diseases including thalassemia, sickle cell anemia, polycythemia rubra vera, chronic myelogenous leukemia, myeloid metaplasia, and hereditary spherocytosis. The EMH is commonly seen at sites such as the abdomen, chest, or epidural space. There are two forms of EMH namely para-osseous in which the normal medullary tissue of the bone marrow ruptures through the bone to present as a para-osseous mass, and "extra-osseous-in which EMH occurs within soft tissue. Para-osseous EMH occurs more frequently in haemoglobinopathies whereas extra-osseous EMH accompanies predominantly myeloproliferative disorders.*(Chute et al.,2004)*

When these pseudotumours are placed paravertebral, they can progress towards the spinal canal and carry a high risk of spinal cord compression with severe neurological symptoms. *(Gologan et al., 2005)*

So the aim of the present study was to assess the problem of spinal cord compression related to EMH in β thalassemia patients.

As regards the demographic data of the studied thalassemic patients in the present study, there was a non significant difference between the two thalassemic groups (major and intermedia) as regards sex, age, consanguinity, cardiac and hepatic affection, although there was a highly significant difference between the two groups as regards family history of anaemia, splenectomy and age of first blood transfusion. Positive family history of anemia was found in 47.5% of patients with thalassemia major and only in 15% of patients with thalassemia intermedia, this goes with the genetic mode of inheritance of the disease as it is a recessive inherited disease. (Low et al., 2005)

Splenectomy was done in 80% and 30% in patients with thalassemia major and thalassemia intermedia respectively. The increased rate of splenectomy in thalassemia major patients is explained by that the constant exposure of the spleen to red cells with inclusions consisting of precipitating globin chains, give rise to the phenomenon of work hypertrophy so progressive splenomegaly occurs and exacerbate the anaemia.*(Weatherall et al., 2000)*

While huge splenomegaly is not a constant feature of thalassemia intermedia so as long as the haemoglobin level remains acceptable and the patient is feeling well, there is no need for splenectomy in thalassemia intermedia. *(Taher, 2006)*

Concerning the age of first blood transfusion, it was 0.8 ± 0.6 years and 7.3 ± 3 years old in patients with thalassemia major and thalassemia intermedia respectively. Since β chain synthesis replaces γ chain synthesis during the first months of life, severe forms of β thalassemia (thalassemia major) usually present during the first year when the normal physiologic anemia of the new born fails to improve. On the other hand one of the hall marks of β

thalassemia intermedia is its late presentation compared to transfusion depended forms of the disease (thalassemia major). *(Steinberg et al., 2001)*

In the present study patients with under weight (less than tenth centile for age) account for 20% and 10% of patients with thalassemia major and intermedia respectively, and patients with short stature (less than tenth centile for age) were 32.5% and 15% for patients with thalassemia major and intermedia respectively.

Parallel to our results, *Low et al*. *2005* reported that 18% of thalassemia major patients had short stature.

Despite medical advances, growth failure remains a significant clinical problem in patients with thalassemia. Chronic tissue hypoxia and iron toxicity from transfusional hemosiderosis have been implicated as major causes of growth retardation in those patients. Also progressive accumulation of iron in the endocrine glands in thalassemic patients results from transfusional hemosiderosis. *(Low, 2001)*

Shalitin et al., (2005) reported that high serum ferritin levels during the first decade of life in thalassemic patients predict short stature which indicate that hemosiderosis is an important factor affecting growth of those patients.

Other causes of growth failure in thalassemics may be due to the toxic effects of desferrioxamine (epiphyseal dysgenesis), or the development of other endocrinopathies such as GH insufficiency or primary hypothyroidism. *(Wu et al., 2003)*

Also we observed that delayed puberty was more frequently observed in thalassemia major comparable to thalassemia intermedia patients (52.5% in thalassemia major and 18.2% in thalassemia intermedia).

Similar to our results *Shamshirsaz (2003)* reported that 77% of thalassemia major patients had delayed puberty.

Impaired puberty is the most common endocrine abnormality reported in thalassemics. This abnormality is related to iron overload (hemosidrosis) and other factors responsible for organ damage. Among these factors is liver damage due to viral infections, chronic anemia and individual susceptibility to damage from iron overload. Zinc deficiency is considered also as one of the main factors contributing to growth and puberty disorders in thalassemic patients. *(Shamshirsaz et al., 2003)*

Impaired puberty is defined as more than 2 SD delay in pubertal development beyond the mean for their sex. Irregular menstrual cycles are characterized by an unpredictable and variable interval between menses which always occurs more frequently than every 3 months. *(Cappellini et al., 2000)*

Regarding the laboratory parameters of the studied groups a highly significant difference was found between the two groups (major and intermedia) with mean Hb F 49.2% versus 16%, mean pretransfusion Hb level 6.8 mg/dl versus 7.6 mg/dl, mean serum ferritin in the last year 2075 μg/ml versus 810 μg/ml in thalassemia major and intermedia respectively.

Mean serum ferritin was much higher in thalassemia major patients than thalassemia intermedia due to their more frequent need for blood transfusion. *(Taher, 2006)*

Although the rate of iron accumulation in thalassemia intermedia is slow, the complications do occur later in life. Iron

overload occurs even in untransfused TI patients because of ineffective erythropoiesis, peripheral RBCs breakdown and increased GI absorption. *(Taher, 2006)*

In the present study osteoporosis is detected by decreased trabeculations in the lumber region showed by CT scanning.

The prevalence of osteoporosis was significantly higher in patients with thalassemia major than those with thalassemia intermedia. Also the prevalence of osteoporosis was significantly higher in older patients (23.5% in β thalassemia major patients aged < 15 years old versus 82.6% β thalassemia major patients aged >15 years old and in 50% of β thalassemia intermedia patients aged > 15 years old. None of the thalassemia intermedia patients < 15 years old had osteoporosis).

Parallel to our results, a longitudinal study done by *Voskaridou et al (2001)* showed that the prevalence of osteoporosis in the lumbar region in patients with β thalassemia major was 50.7% with significantly higher percentage in older patients.

With the improved survival of thalassemic patients, metabolic bone disease accounts for significant morbidity in this population. Thalassemic osteopathy is thought to be multifactorial, attributable to nutritional (e.g. Ca-vit D deficiency), hematological (anemia, bone marrow expansion, haemosiderosis), hormonal (endocrine deficiencies) and pharmaceutical factors (e.g. desferrioxamine).*(Protonotariou et al.,2000)*

Trace metals deficiencies in patients with thalassemia major have been under debate. Trace minerals have been shown to

influence growth and hormones at several levels, and zinc deficiency which may be considered as a causative factor for osteoporosis and endocrinopathies. Low levels of vitamin D were also reported in thalassemic patients. *(Bielinski et al., 2003)*

Taher et al. (2006) reported that ineffective erythropoiesis leads to severe consequences. The efforts to compensate for ineffective erythropoiesis and anemia may be associated with massive erythroid marrow hypertrophy in medullary and extramedullary sites. In long bones, marrow expansion results in cortical thinning and pathological fractures.

In β thalassemia major patients, the relation between osteoporosis with transfusion frequency and with transfusion index were highly significant and significant respectively (i.e. the percent of osteoporosis was higher in patients with decreased transfusion frequency and decreased transfusion index). Both relations were non significant in β thalassemia intermedia patients. While the relation between mean Hb level and osteoporosis was significant in both groups (i.e. the percent of osteoporosis was higher in patients with low mean Hb level).

There was a non significant relation between chelation adequacy and osteoporosis in both groups, lastly there was a significant relation between mean serum ferritin and osteoporosis in β thalassemia major patients (i.e. the percent of osteoporosis was higher in patients with high serum ferritin).

Regarding the main topic of the present study which was EMH, 60 thalassemic patients were screened for the presence of EMH by thorough neurological examination, CT scanning on lumbosacral region and suspected patients (patients with increased

soft tissue density by CT) were subjected to MRI study on the dorsolumbar region.

By clinical examination we found that one out of 17 patients in group 1 (β thalassemia major patients <15 years old) had neurological findings and proved to have EMH, 7 out of 23 patients of group 2 (β thalassemia major patients >15 years old) had neurological findings only 3 of them proved to have EMH. Regarding the 10 patients in group 3 (β thalassemia intermedia patients <15 years old) none of them had neither neurological findings nor EMH, in group 4 (β thalassemia intermedia patients >15 years old) 4 out of 10 patients had abnormal neurological findings and proved to have EMH.

Regarding the four patients with thalassemia major aged more than 15 years old which had abnormal neurological findings without EMH by radiology, this could be explained by that neurological findings in thalassemic patients may be attributed to other central nervous system complications like convulsions, transient ischemic attacks, cerebral headaches, paresthesias, hyporeflexia, hemiplegia, and hemiparesis. These findings have been attributed to the release of vasopressins after multiple transfusions, leading to hypertension, encephalopathy and haemorrhage. With a better knowledge of natural inhibitors of coagulation, it is now known that there is an increased tendency to thrombosis in haemolytic anemias, especially in thalassemia major. Deficiencies of protein C, protein S and antithrombin III have some role in this prothrombotic tendency. Also it was reported that thalassemic RBCs may provide a source of negatively charged phospholipids which can increase thrombin generation. (*Akar et al., 2000)*

The differential diagnosis of extradural lesions compressing neural structures in the intervertebral foramen mainly includes herniated discs and schwannoma. However, the onset of neurological symptoms in a patient with an underlying blood disease should promptly raise a high clinical suspicion of an extramedullary hemopoietic process. Currently, CT scans and MR imaging are the preferred modalities for establishing the diagnosis and ruling out other possibilities. EMH express low signal intensity on both CT and MRI. These findings are characteristic of iron deposition. *(Tsitsopoulos et al., 2007)*

CT scan was used as a screening technique due to its sensitivity and the relative low cost when compared to MRI. *(Sule et al., 2002)*

MRI was considered as modality of choice in diagnosis of EMH and the gold stranded allowing precise diagnosis and spreading of EMH. *(Chourmouzi et al., 2001)*

In the present study we found that EMH were found in 13.3% of our patients, mostly in patients aged > 15 years old (7 out of 8 patients). Parallel to these results, a study done by *Aliberti et al., 2000* found that although EMH is a common finding in thalassemic patients, an intraspinal location is uncommon, being found in 11 to 15% of cases. Another study done by *Gologan et al., 2005* found that most thalassemic patients found to have EMH were aged above 20 years old. They reported a case at Romania with TI and EMH aged 44 years old and with mean Hb level 7 gm/dl. In their report they stated that symptomatic EMH is an unusual occurrence in childhood and adolescence, probably due to a better quality of the bone at that age.

EMH is a common compensatory phenomenon associated with chronic hemolytic anemia. Abnormal hemopoietic tissue usually develops in sites involved in hemopoiesis during fetal development, such as the spleen, liver, and kidneys; however, other locations including the paraspinal region may be involved. *(Tsitsopoulos et al., 2007)*

At *2002 Tze-Ching et al*. found that spinal EMH sufficiently severe to cause SCC rarely occurs and they reported an incidence of 0.8% in thalassemic patients. The pathogenesis of this disease is controversial. This has been attributed to the extension of hyperplastic marrow through the thinned-out trabeculae at the proximal end of the bones. It is also believed that the embryonic cells that rest within the epidural space get transformed into haematopoietic tissue. *(Ghosh et al., 2005)*

In the present study EMH was found in 20% and 10% of patients with thalassemia intermedia and thalassemia major respectively despite nonsignificant difference in their ages. This could be explained by that thalassemia intermedia patients are not usually treated with regular transfusion therapy as the medullary and EMH are able to maintain haemoglobin concentration above a reasonable level, in contrast to individuals with thalassemia major whose life is dependent upon regular transfusion therapy. Consequently, subjects with thalassemia intermedia demonstrate severe grade of manifestations referable to medullary and extra-medullary hematopoisis. *(Ameri et al., 2003)*

We found that the relation between the presence of EMH and inadequate chelation was significant in both groups of patients (thalassemia major and intermedia) and the relation between increased mean serum ferritin and EMH was significant in patients with β thalassemia major and highly significant in patients with β thalassemia intermedia. Mean serum ferritin in patients with EMH

was 3333 μg/L versus 2250 μg/L in patients with β thalassemia major and intermedia respectively. This may be explained by their non compliance to the treatment (blood transfusion and chelation) and also it has been suggested that the liability for complications increases with mean serum ferritin level above 2000 μg/L.*(Chan et al., 2001)*

This goes in parallel with many case report studies of EMH in thalassemic patients which had a high mean serum ferritin level above 2000 μg/L as in the case reported by *Cario et al. 2002*, with mean serum ferritin level 2844 μg/L.

It is obvious from our results that the presence of EMH was highly related with low mean Hb level (mean haemoglobin in patients with EMH was 5.8 mg/dl) which matches a case report done by Ghosh *et al.* 2005 for a 16 years old thalassemic patient who complained of progressive weakness of both lower limbs and was proven to be due to EMH. His mean haemoglobin was 6.5 mg/dl.

The relation between decreased transfusion frequency per month and low transfusion index with EMH was highly significant in β thalassemia major patients. This explains why EMH can be prevented and treated by the institution of regular transfusion therapy, which corrects anaemia and thereby, abolishes the stimulus for EMH and the patients general condition get better, the liver and spleen get smaller. *(Habebzadeh et al., 2005)*

Although no relation between decreased transfusion frequency per month and low transfusion index with EMH was detected in β thalassemia intermedia patients and this could be explained by their irregular attendance for blood transfusion or due to the small number of the patients of this group, however the transfusion frequency and transfusion index were still lower in patients with β thalassemia intermedia and EMH than patients in the same group without EMH.

Introduction:

Beta thalassemia is an inherited disorder that affects the beta globin (protein molecules) chains. These chains are required for the synthesis of haemoglobin A (a compound in the blood that carries oxygen to the cells and carbon dioxide away from the cells). A decrease of beta globin chains causes early destruction of the red blood cells. There are four types of the disorder and they range in severity of symptoms.

The thalassemias were first discovered by Thomas Cooley and Pearl Lee in 1975. Early cases of the disease were reported in children of Mediterranean descent and therefore the disease was named after the Greek word for sea, thalasa. (Thompson et al, 1991)

Extramedullary haematopoiesis (EMH) is a compensatory phenomenon that occurs in patients with haematological disorders when bone marrow function is not sufficient to maintain the circulatory demand. It has been seen in different types of severe anaemia, such as polycythemia, leukaemia and lymphoma, and after bone marrow irradiation, poisoning or neoplastic conditions.

The most common sites of EMH are organs that have physiological haematopoiesis during embryonic life, especially the liver and spleen. Other sites of diffuse compensatory EMH include lymph nodes, adrenal glands, kidneys, breast, dura mater, adipose tissue and skin.(Gemenist et al, 1989)

Extramedullary haematopoiesis generally occurs in a variety of haematological disorders where the normal functioning of the blood forming organs is disturbed. It is a common manifestation in thalassemia where it occurs as a compensatory phenomenon in order to combat long standing anaemia. Spinal cord compression as a consequence of extramedullary haematopoiesis in the

intraspinal epidural space is an extremely rare complication, though this complication has been reported more commonly in thalassemia. (Konstantopoulosk, 1992)

The diagnosis and differential diagnosis in thalassemic patients presenting with spinal cord compression is not very difficult with the modern imaging techniques i.e. CT scan and magnetic resonance imaging (MRI). In our study, the diagnosis was based upon clinical presentation and was confirmed by CT. (Ben Rejad and Haouala , 1992)

The first description of spinal cord compression by EMH dates from 1954. Since then, about 60 cases have been reported, most of them in intermediate □-thalassemia patients. This complication has mainly been observed in the thoracic segment of the spinal cord but the reason for this predilection remains uncertain. (Kaufmann et al, 1991)

The development of haematopoietic tissue in the vertebral canal is probably due to a bone marrow expansion leading to spinal cord compression. On CT and MRI, the EMH looks like a well-delimited lobular soft tissue with no erosion of the adjacent bone structures. Management strategies have included radiotherapy (RT), laminectomy, and transfusion therapy. Spontaneous recovery with no therapeutic intervention has also been reported, but may take several months to occur and is subject to frequent recurrence. Patients treated only with transfusion have initially showed improvement, but with frequent recurrence. (Kaufmann et al, 1991)

RT has been reported to yield excellent results with prompt neurological response since the haematopoietic tissue is radiosensitive and relatively small doses of radiation are needed. Complete recovery is achieved in as short a time as 3 to 7 days. (Singounas et al, 1991)

There is still controversy regarding the optimal management

of these patients. Extramedullary haematopoiesis is a benign lesion and epidural location is exceptional but could lead to severe neurological complications. An early diagnosis avoids major surgery for debilitated patients. (Munn et al, 1998)

Aim of the work:

The aim of the present study is to assess the problem of spinal cord compression related to extramedullary haematopoiesis in Beta thalassemia patients.

Subjects and methods:

Study population:

The study will include 60 patients with Beta thalassemia who will be recruited at random from the regular attendance of the Pediatric Haematology Clinic at the Children Hospital Ain Shams University.

They will be classified into four groups:

- Group A :

  Patients with Beta thalassemia major aged less than 15 years.

- Group B :

  Patients with Beta thalassemia major aged more than 15 years.

- Group C :

  Patients with Beta thalassemia intermedia aged less than 15 years.

- Group D :

  Patients with Beta thalassemia intermedia aged more than 15 years.

Methods:

All patients will be subjected to the following:

A. A structured questionnaire will be planed to fulfil the following data:

a. Demographic data :

Name, age, sex, address, consanguinity, socioeconomic class.

b. Transfusional history:

- ❖ age of first transfusion,
- ❖ amount of blood in every transfusion,
- ❖ type (whole blood or packed RBCs),
- ❖ frequency
- ❖ calculation of the transfusion index in packed RBCs ml/Kg/year.

c. Chelation history:

- ❖ drug taken,
- ❖ dose.

d. History of haemolytic crisis.

e. Past history of splenectomy, hepatitis (type and date of diagnosis).

f. Family history of anaemia.

g. Symptoms of cardiac affection (palpitation or dyspnoea)

h. History of renal or hepatic affection.

i. Full neurological data about:

1-motor system:

weakness, tone, muscle state, fasciculation, extra pyramidal manifestations, cerebellar manifestations.

2-Sensory system:

-superficial sensations (pain, temperature and touch)

-deep sensation (position, movement and vibration)

3-Cranial nerves

4-Hypothalamus symptoms as diabetes insipidus, hypersomnia and polyphagia

5-Sphincteric affection.

B. Examination:

Thorough clinical examination with particular emphasis on:

a. Anthropometric measures:

- ❖ weight in kilograms
- ❖ height in centimetres.

And the values will be plotted against percentiles for age and sex.

b. Tanner staging for sexual maturity rating.

c. Complexion and signs of vitality

d. Chest , heart and abdominal examination:

e. Full neurological examination:

- ❖ Motor system:

1-Tone:

ankle, knee, hip, wrist, elbow and shoulder.

2-Muscle state:

-atrophy

-hypertrophy.

3-Power.

4-Fasciculations.

5-Reflexes:

-deep reflexes (tendon jerk)

-superficial reflexes.

6-Extrapyramidal ⟹ involuntary movements.

7-Cerebullum ⟹ intentional tremors and dysmetria.

- Sensory system:

1-Superficial sensation:

sensation of pain, temperature and touch.

2-Deep sensation:

sense of position, movement and vibration.

3-Cortical sensation:

steriognosis, tactile localization and tactile discrimination.

- Cranial nerves

C. Investigations done will include:

Laboratory investigations:

-Complete blood count

-Haemoglobin electrophoresis at time of diagnosis and at the onset of the study

-Liver function tests

-Renal function tests

-Serum iron and ferritin.

Radiological investigations:

- CT scan on dorsal and lumbosacral region will be performed to all groups of patients.

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Summary

Thalassemia is a hereditary form of anemia resulting from defects in hemoglobin production. Beta thalassemia, a quite common disease in Mediterranean populations, affects multiple organs and is associated with considerable rates of morbidity and mortality.*(Cunningham et al., 2004)*

EMH is a common compensatory phenomenon associated with chronic hemolytic anemia. Abnormal hemopoietic tissue usually develops in sites involved in hemopoiesis during fetal development, such as the spleen, liver, and kidneys; however, other locations, including the paraspinal region, may be involved. This pathophysiological response is generally asymptomatic; however, if the hemopoietic tissue exerts pressure on neural structures, it may cause neurological symptoms.*(Tsitsopoulos et al., 2007)*

An intraspinal location of EMH is uncommon and is found in only 11-15% of cases.*(Salehi et al., 2004)*

The aim of the present study was to assess the problem of EMH in thalassemic patients both clinically and radiologically. This study included 60 thalassemic patients divided into 4 subgroups (17 Patients with Beta thalassemia major aged less than 15 years, 23 Patients with Beta thalassemia major aged more than 15 years, 10 Patients with Beta thalassemia intermedia aged less than 15 years and 10 Patients with Beta thalassemia intermedia aged more than 15 years)

They were subjected to full history taking, thorough clinical examination specially neurological examination, laboratory investigations and radiological investigations which were :

a) Lumbosacral CT scan for all patients as a screening technique.
b) MRI for suspected patients to confirm the presence of EMH.

Our results revealed that EMH was found in 13.3 % of the studied thalassemic patients (8 out of 60 patients) with increasing incidence in β thalassemia intermedia patients (20%) than β thalassemia major patients (10%).

The presence of EMH was more likely to be found in older patients.

EMH was found to be related to inadequate chelation and high mean serum ferritin levels. This relation was more significant in patients with β thalassemia major than those with β thalassemia intermedia. It was found to be also related to low mean hemoglobin level, decreased transfusion frequency per month and decreased transfusion index.

5% of the patients in the study had neurological symptoms without radiological evidence of EMH, so other causes of neurological insult in thalassemic patients had to be considered (thromboembolism, encephalopathy and haemorrhage).

الملخص العربي

أنيميا البحر المتوسط من الأمراض الوراثية الناتجة عن خطأ في تصنيع الهيموجلوبين. هذا المرض شائع في دول البحر المتوسط ويؤثر على أعضاء متعددة ويصاحب بالعديد من المضاعفات .

يعتبر التصنيع الدموي الخارج النخاعي عملية تعويضية عن الأنيميا المزمنة. خلايا التصنيع الدموي الغير طبيعية عادة ما توجد في الطحال ، الكبد ، الكلى ، وأحيانا تكون في أماكن أخرى مثل منطقة حول العمود الفقري. هذه العملية عادة ما تكون غير مصاحبة بأعراض ولكن إذا ضغطت هذه الخلايا على خلايا عصبية من الممكن أن تسبب أعراض عصبية .

إن وجود هذه الخلايا حول العمود الفقري غير شائع ، يحدث في ١١-١٥% .

الغرض من هذه الرسالة هو تقييم مشكلة التصنيع الدموي الخارج النخاعي في مرض أنيما البحر الأبيض المتوسط .
هذه الدراسة شملت ٦٠ مريضا مقسمين إلى ٤أجزاء .

جميع المرضى تم عمل الآتي لهم :

- أخذ تاريخ مرضى مفصل .
- كشف عام خاصة كشف على الجهاز العصبي .
- فحوصات معملية .
- أشعة مقطعية على الفقرات القطنية .
- رنين مغناطيسي للمشتبه بإصابتهم بالتصنيع الدموي الخارج النخاعي .

لقد أسفرت نتائجنا عن أن التصنيع الدموي الخارج النخاعي يوجد في ١٣,٣% من المرضى بنسبة متزايدة في مرض أنيميا البحر الأبيض المتوسط المتوسطة عن العظمى ، وأن هذه النسبة تتزايد مع تقدم المريض في السن .

إن التصنيع الدموي الخارج النخاعي مرتبط بزيادة نسبة الحديد في الدم وكذلك بعدم كفاية نقل الدم وقلة نسبة الهيموجلوبين في الدم .

إن المرضى الذي أثبتت إصابتهم بالصنيع الدموي الخارج النخاعي يعانوا من أعراض عصبية غير محددة (آلام في الظهر ، تنميل في الأطراف السفلى) .

إن ٥% من المرضى في هذا البحث يعانوا من أعراض عصبية بالرغم من عدم وجود تصنيع دموي خارج النخاعي سواء بالأشعة المقطعية أو بالرنين المغناطيسي. لهذا فإن الأسباب الأخرى لوجود أعراض عصبية في هؤلاء المرضى يجب أن توضع في الاعتبار